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ON THE RELATION OF THE ISLANDS OF LANGERHANS TO GLYCOSURIA.

By W. G. MacCallum, M. D.,
Professor of Pathological Physiology, Johns Hopkins University, Baltimore.

(From the Hunterian Laboratory.)

In their earlier papers upon diabetes mellitus, Opie and others showed that in all probability the islands of Langerhans are of paramount importance in maintaining the normal carbohydrate metabolism, and that in certain cases of diabetes with intense glycosuria the lesion may apparently consist in their being destroyed while the rest of the pancreas is intact. The fact is, however, recognized that there are many cases of diabetes in which this specific lesion does not occur, and there are many who hold that it is far from proven that the islands of Langerhans have any such special function, and that diabetes is rather the result of injury to the whole tissue of the pancreas. This whole question has been ably reviewed by Sauerbeck,[1] to whose paper the reader may be referred. It is of course desirable that we should know precisely the function of these islands of tissue, and many experiments have been devised to throw light upon the subject, but the difficulties are such that as yet the evidence is not conclusive. They are so small and numerous and so widely scattered throughout the tissue of the pancreas that there is no question of separating them mechanically and investigating their activities, as has been done with the other so-called organs of internal secretion.

It is known, however, that if the ducts of the pancreas be ligated so that the secretion of that gland is obstructed from passing into the intestine, there follow certain digestive disturbances and injuries to the gland, but there is no disturbance of carbohydrate metabolism and no glycosuria. Indeed, even though the animal live for some time so that a marked scarring and atrophy of the obstructed gland is produced,

[1] Sauerbeck, Lubarsch and Ostertag: Ergebnisse d. allg. Path. u. path. Anat., IX., 1.

there need be no glycosuria, although as Pratt has recently shown the assimilation limit for carbohydrates may be lowered. This is generally ascribed to the fact that although such obstruction to the ducts causes the atrophy of the secreting acini, the islands of Langerhans, not being connected with the ducts, do not suffer, and indeed are usually found intact in the scar tissue which replaces the gland. A similar explanation for the absence of glycosuria is most plausible in those experiments of Minkowski in which portions of the pancreas were transplanted or dislodged from their usual position and from all connection with the duct, the remainder being then removed.

Such experiments seem to promise a satisfactory solution of the question if it is true that by such means the secreting tissue of the pancreas can be made to atrophy completely; for then if the islands of Langerhans really remain intact, they might finally be secured in a pure state so that their specific function could be studied.

The following experiment, which was planned from this point of view, will be given for what it is worth, although it will be seen that even under the most favorable conditions a perfectly clean-cut result can hardly be expected. In most respects it resembles the experiments of Minkowski or those in which the whole pancreas is ligated and separated from the intestine.

It seemed that the chief objection to the latter mode of conducting the experiment lay in the fact that if atrophy of the secreting portion of the gland were to be complete, the dog must be kept in good condition for a very long time after the ligation of the duct, which must be difficult or impossible if the whole pancreas is thrown out of connection with the intestine. For this reason the dog was left with half of the pancreas, or rather more, in the normal condition, while the remainder was separated after ligating its duct and allowed to atrophy. It was proposed to allow the dog to live for a long time in this condition and then study the function of this atrophied portion, which should then consist presumably of islands of Langerhans only.

The protocol of the experiment was briefly as follows:

Dog 76, 1908. Stout, brown and black male.

October 8, 1908. One of the two branches of the pancreas, constituting rather more than one-third of the whole gland, was separated from the rest by the passage of two ligatures about the gland, which was cut through between them. These ligatures of black silk were intended to act as landmarks later. The ligated portion lying in the mesentery was pushed back and the omentum tucked about it. The head of the gland was applied to the intestine and the other branch remained untouched.

The dog recovered perfectly from this operation and was quite well all winter, with absolutely no signs of pancreatic insufficiency.

May 9, 1909. Fehling's test for sugar in the urine, negative.

May 10, 1909. Second operation, in which the isolated portion of the pancreas was brought to view. It was easily found by the aid of the black ligatures, but would otherwise have escaped notice, for nothing remained except the faintest opalescence in the mesentery, with the most inconspicuous points of thickening here and there. This area was, however, pretty well outlined by the abundant and peculiarly arranged blood vessels, which formed the most conspicuous feature.

The remainder of the pancreas was quite normal in appearance, and the proximal black silk ligature was found on its stump opposite the atrophied area. This whole mass was extirpated, the vascular supply to the intestine being carefully freed from the head of the pancreas in which it lies embedded. This was done in such a way that one could be quite sure that no vestige of the pancreas remained except the atrophied isolated portion described.

Urine secreted just before the operation showed no sugar, nor did that secreted during the remainder of the day.

May 11. Urine collected during the morning of this day showed no sugar on being tested with Fehling's solution, but on the next day, May 12, the urine contained a considerable quantity of sugar and gave an abundant precipitate with Fehling's solution. This sugar was unfortunately not estimated, but it continued during the next day, May 13, diminishing greatly on May 14. After this, as will be seen from the chart, there was practically no glycosuria, although on some days an inestimably small quantity was excreted, and on May 21 and 22 it was possible to estimate the quantity (0.53 and 0.26 gm.). On these days sugar was found only in the relatively concentrated urine secreted during the night, and not at all in the more dilute urine which was secreted after the daily ration of 500 gm. of water. After this up to May 30 the urine was quite free of sugar, although dextrose was administered in increasing doses to determine the dog's assimilation limit. At first for several days, May 21-22, no food was given, then 5 gm. dextrose on May 23, and 10 gm. on May 24. After that the diet of beef (200 gm.) was resumed, together with the dextrose, which was increased to 20 gm. It was not until 40 gm. of dextrose was given at one dose with the 200 gm. of beef and 500 cc. of water that any glycosuria appeared.

In the urine secreted during the next eight hours there was excreted 1.496 gm. of sugar, while that secreted at the end of the eight hours was absolutely free from sugar. Evidently, therefore, this dog with his atrophied remnant of pancreas could assimilate 38.504 gm. of dextrose when taken at one dose. After this the diet consisted of 200 gm. beef and 500 cc. water, and there was no glycosuria.

On June 1, two days after the excessive dose of dextrose, a third operation was carried out. The dog was fed as usual in the morning and given 500 cc. of water. At 3 p. m., after he had secreted 400 cc. of sugar-free urine, the abdomen was opened under ether anæsthesia, which lasted an hour and 25 minutes. Abundant omental adhesions had formed round the site of the last operation and enclosing the pancreatic remnant, so that its extirpation was not as simple as expected. It was finally plainly outlined, however, and seemed to have grown noticeably thicker than it had been at the last operation. Distinct, though minute, nodular masses could now be seen, richly supplied with blood vessels. A triangular piece of mesentery was excised so as to remove all of this mass, giving it a wide berth. The tissue itself was fixed in formalin for microscopical study. At 8.30 p. m. the dog had secreted 85 cc. of urine rich in sugar, the whole amount containing 0.5720 gm. of sugar. The 125 cc. secreted during the night was much richer, containing more than 6 gm. of sugar.

This intense glycosuria persisted through the next three days, the dog excreting (as seen in the chart) 23.32, 15.95, 5.104 gm. respectively on these days. It is notable that the amount of sugar excreted thus sank rapidly during the days following the operation, and it would have been wise to observe the dog without further intervention for as long as possible, because the question arises as to the part played by the ether anæsthesia in this rather transient glycosuria. All this had not been thought out at the time, however, and it had been planned to study the effect of thyroidectomy upon this depancreatized dog.

Accordingly, on June 5 the dog was again etherized for about 45

minutes and both lobes of the thyroid removed, the two larger parathyroids being left in situ. After this and for the next three days, that is, up to the animal's death, there was no trace of sugar in the urine. It is unlikely, therefore, that the previous etherization was important in producing the glycosuria, since the anæsthesia at the last operation had no such effect.

I can, however, offer no good explanation for the complete disappearance of the glycosuria after the thyroidectomy. It is true that in this dog, accustomed as he was for a long time to a relative insufficiency of the pancreas, the glycosuria after the complete extirpation of the pancreas was rapidly diminishing, and it would have been very desirable to know whether without the thyroidectomy it would have disappeared completely.

This suggests the possibility that if pancreatic insufficiency be slowly enough produced some other organ may supply the alimentary glycosuria. But for the glycosuria following extirpation of the pancreas the experiments quoted by Eppinger, Falta, and Rudinger show a diminution, but not a complete disappearance, after thyroidectomy. I have carried out one experiment in this connection which agrees with their results as contrasted with those of Lorand, who caused complete cessation of the glycosuria following pancreatectomy by thyroidectomy.

The experiment was briefly as follows:

Dog 79, 1909. June 10. Whole pancreas extirpated. Urine normal.

June 11. Urine contains 12 gm. sugar.

June 12. Urine contains 32.68 gm. sugar. Both thyroids extirpated at noon, parathyroids left.

June 13. Urine contains 16.58 gm. sugar. Dog died at end of this day.

Date.	Operation.	Diet.	Water.	Amount urine.	Fæces.	Sugar.	Total N.	$\frac{D}{IV}$ ratio.	NH_3N.	Weight.
May 10	Extirp. of intact portion of pancreas.	General.	.....	300 gr.	.....	.....	.....	.....	.....	.....
" 11	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
" 12	.....	.....	.....	.....	.....	Abundant.	.....	.....	.....	.....
" 13	.....	.....	.....	.....	.....	Abundant.	.....	.....	.....	.....
" 14	.....	.....	.....	.....	.....	Less.	.....	.....	.....	.....
" 17	.....	.....	.....	.....	.....	Minimal.	.....	.....	.....	.....
" 18	.....	.....	.....	.....	.....	Normal.	.....	.....	.....	.....
" 19	.....	.....	.....	Small.	Voluminous, pale.	Minimal.	.....	.....	.....	.....
" 20	.....	200 gr. meat.	500 gr.	.....	Abundant.	None.	.....	.....	.....	.....
" 21	.....	0	500	240	Fatty stools.	0.53 gr.	.....	.....	.....	.....
" 22	.....	0	500	795	Fatty.	0.264 gr. (only in conc. urine).	.....	.....	.....	20¼ lbs.
" 23	.....	5 gr. dextrose.	500	435	.....	0	.....	.....	.....	.....
" 24	.....	10 gr. dextrose.	500	465	.....	0	.....	.....	.....	.....
" 25	.....	10 gr. dextrose, 200 gr. beef.	500	515	0	0	.....	.....	.....	.....
" 26	.....	20 gr. dextrose, 200 gr. beef.	500	490	Abundant undigested meat.	0	.....	.....	.....	.....
" 27	.....	200 gr. beef.	500	602	.....	0	.....	.....	.....	.....
" 28	.....	.....	.....	.....	Nearly normal.	0	.....	.....	.....	.....
" 29	.....	40 gr. dextrose, 200 gr. beef.	500	285	.....	0	.....	.....	.....	19¼ lbs.
" 30	.....	200 gr. beef.	500	630	.....	14.96 gr.	7.88 gr.	1.9 gr.	.....	.....
" 31	.....	200 gr. beef.	500	175 (some lost)	Little.	0	.....	.....	..... gr.	.....
June 1	2d operation, extirpation of islands.	200 gr. beef.	500	575	.....	0	5.31	.....	0.46308	18¾ lbs.
" 2	.....	200 gr. beef.	500	610	.....	6.860 gr.	6.58	1.04	0.2728	.....
" 3	.....	200 gr. beef.	500	636	.....	23.32 gr.	7.60	3.06	0.77308	.....
" 4	.....	200 gr. beef.	500	725	.....	15.95 gr.	10.55	1.5	0.64706	17½ lbs.
" 5	Thyroidectomy.	200 gr. beef.	500	755	.....	5.104 gr.	7.04	0.7	0.68667	.....
" 6	.....	200 gr. beef.	500	530	.....	0	7.42	.....	0.39193	16½ lbs.
" 7	.....	200 gr. beef.	500	528	.....	0	10.02	.....	0.493	.....
" 8, died	.....	.....	300	432	.....	0	3.65	.....	1.831	.....

function and maintain carbohydrate metabolism. An analogous instance seems to have been furnished by the dog operated upon by Dr. Halsted in which, after complete extirpation of the parathyroids, a parathyroid was transplanted, and the dog was kept alive by a microscopic fragment of this tissue for a year. After the extirpation of this infinitesimal mass he lived for weeks and was finally killed. The most minute search failed to reveal any more parathyroid tissue. One received the impression that after all the action of these glands is not absolutely specific, and that possibly their function may be assumed at need by others.

As to the part played by the thyroidectomy, the following may be said: It is known, as Eppinger, Falta, and Rudinger have pointed out, that extirpation of the thyroid gland decreases glycosuria produced by adrenalin when the pancreas is intact. Grey and de Sautelle have proven the same thing for the glycosuria following ether anæsthesia, and McCurdy for

Here there was a diminution in the glycosuria, but no such complete disappearance as in the dog the subject of our first experiment.

Whether the thyroidectomy influenced it or not, it remains to be explained why there should be such a complete cessation of glycosuria in a dog entirely deprived of his pancreas. Of course a cessation of glycosuria occurs in diabetics on the advent of an infectious or inflammatory process and under other circumstances before death, but in those cases too the explanation is obscure.

New difficulties arise when we come to the microscopical study of the atrophied portion of the pancreas removed at the third operation, for it is not easy to say with certainty whether the curious tissue found there is composed only of island of Langerhans cells or partly of distorted and shrunken pancreatic cells. A priori it would seem impossible that there should be an absolutely complete disappearance of the pancreatic tissue,

and the persistence of abundant ducts serves to make this more evident. The tissue consists of numerous minute strands and masses abundantly supplied with blood vessels and lying in the loose fibrous tissue of the mesentery. There is only one type of cell aside from those definitely forming the walls of the persistent ducts. These cells are arranged in long strands or very commonly in balls or acinus-like masses, or are quite irregularly strung together. The outline of each group is very irregular, but the groups are far larger than any normal island of Langerhans. In the places where the cells are grouped in acinus-like balls and where there are ducts scattered among them, it is hard to avoid the idea that they are remnants of pancreatic tissue. Elsewhere, however, where the same cells are arranged irregularly or in strands, this impression is not received. In no particular, however, do the cells themselves resemble the normal pancreatic cells. Instead of a protoplasm filled with granules we have a ragged, vacuolated, unstained protoplasm. Instead of a nucleus with definite red-staining nucleolus, as is found in the pancreatic cells, we have one in which no nucleolus shows. On the other hand these peculiarities are exactly those of the cells of the islands of Langerhans, and in every particular the cells are identical morphologically with those constituting the normal islands. The normal islands of Langerhans in the dog are not sharply outlined, and their cells are often clumped together into small acinus-like balls.

On the whole, although such difficulties exist, it seems to me that the evidence is such as to show that we are almost certainly dealing here with very much enlarged and coalescent islands of Langerhans, although there are interspersed remnants of the atrophied pancreas in the form of ducts and possibly also of acini, so shrunken as to be no longer recognizable or functional. Here again further studies to show the course of the anatomical changes in the dog's pancreas after ligation should be carried out.

Nor was the result of the operation for the extirpation of the pancreas an absolutely clean one, for at the autopsy there were found about the duodenum two minute fragments of pancreatic tissue in a good state of preservation and evidently undergoing hypertrophy. The larger of these was about 3 mm. in diameter, and had apparently reformed itself about the stump of the duct. The other much smaller fragment had grown in the substance of the wall of the intestine so as to have been quite inaccessible at the time of the operation. This minute fragment, too, sent duct-like structures into the intestinal mucosa, but such infinitesimal portions of a large organ like the pancreas seem hardly sufficient to obscure the results of the experiment. Indeed they were discovered only by microscopical examination. It would be necessary, however, in order to prevent such an occurrence, to resect the portion of the intestine with which the pancreas comes into relation.

The study of the nitrogen output gave no striking result, unless it be in the terminal increase of the ammonia in the urine, which was accompanied by an excretion of diacetic acid.

The condition of the stools is, however, of interest, for although for a time after the extirpation of the secreting portion of the pancreas they became very voluminous and on certain days consisted almost entirely of fat, they later became quite normal in appearance. During the whole of the last two weeks of the animal's life the food consisted of beefsteak which contained a good deal of fat; but although there were sometimes evidences of incomplete digestion of the beef, the stools did not again assume the vaseline-like consistency which they showed a short time after the extirpation of the pancreas. One receives the impression that here too a compensatory process in brought about, through which the fat-splitting action of the pancreatic juice is gradually replaced by a similar ferment produced elsewhere, probably in the intestine itself.

All of these results lead one to pause before accepting as complete the results of experiments upon these chemical processes which have lasted over only a few days. Whatever be the specificity of the action of certain organs in the normal state of the body when there is a satisfactory response on all sides to the division of labor, it may well be that when one of these organs is disabled or destroyed others can, *if time be allowed*, take up its functions more or less satisfactorily.

Résumé.

When a portion of the pancreas is separated from the rest and its duct ligated, it undergoes extensive atrophy, a tissue remaining which is apparently composed of enlarged islands of Langerhans and the remnants of pancreatic ducts.

If the rest of the pancreas be removed, this atrophied remnant is capable of warding off glycosuria even when considerable amounts of dextrose are ingested. When it itself is removed also, glycosuria appears at once spontaneously. Whether the glycosuria would persist until the death of the animal remains to be determined, but this experiment suggests the possibility that there may be some compensation on the part of other organs, both with regard to glycosuria and the faulty assimilation of fat after the loss of the pancreas. The experiment in so far as it was successful was intended as a demonstration of the specific control of carbohydrate metabolism by the islands of Langerhans.

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TUBERCULOSIS OF THE PARATHYROID GLAND AND ITS RELATION TO THE OCCURRENCE OF TETANY IN TUBERCULOUS MENINGITIS.

By M. C. WINTERNITZ, M. D.,
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During the past year two patients suffering with tetany as a terminal complication of acute miliary tuberculosis have come to autopsy at the Johns Hopkins Hospital. It is known that such symptoms may occur in tuberculous meningitis, and in fact it seems that tetany may occur in tuberculosis even where meningitis can be excluded. With the recent development of our knowledge concerning the function of the parathyroid glands, it is not unnatural that observers should search for lesions in these organs to explain if possible the convulsions.

Within the past few years Carnot and Delion have reported a case of tetany occurring in general tuberculosis, where meningitis could be excluded at autopsy. In their case only one parathyroid gland was diseased, but they were inclined to ascribe the tetany to that lesion. Since their article appeared four other cases have been recorded, one by Benjamin, two by Verebély, and one by Eggers. In all of these cases there were definite though slight tuberculous lesions involving one parathyroid gland. In all of the cases there was a generalized tuberculosis, but in none of them had any symptoms of tetany been observed. These authors, especially Eggers, take exception to the explanation offered by Carnot and Delion concerning the relation of the parathyroid lesion to the occurrence of tetany. They do not think the involvement of one gland sufficient to account for the tetany, since the individual still had at least two normal glandules remaining.

It is with the hope of throwing some light upon the occurrence of tetany in tuberculosis with or without the involvement of the parathyroid glands that the following two cases are reported:

CASE I.—M. L., colored female, age 21 years, was admitted to the medical clinic of the Johns Hopkins Hospital at midnight on the 9th of July. No history could be obtained, as the patient was in deep coma from which it was impossible to arouse her. There was a conjugate deviation of the eyes to the right; the right arm and hand were flexed on the chest, but were not spastic. The hand was occasionally contracted, assuming the obstetrical position. The right thigh and knee were flexed, while the extremities of the left side were straight. Pressure over the lower end of the right upper arm produced typical tetanic contractions of the forearm and hand. These signs could be elicited to a less extent when pressure was made upon the left arm.

The examination of the lungs showed a limitation of movement of the right side. Here the vocal fremitus was increased and the percussion note was almost flat. The breath sounds were distant and tubular in quality over the entire right side. At the left apex there was likewise a slight impairment of the percussion note, and here the breath sounds were tubular, many fine râles being heard. The examination of the heart and abdomen revealed nothing of note.

During the night the patient became even more profoundly comatose. At frequent intervals there were general epileptiform convulsions lasting from one to two minutes. During the convulsions the respirations were shallow and the patient became cyanotic. There were fibrillary contractions of the tongue. In the forenoon the attacks continued at frequent intervals. Between them there was almost complete relaxation. At 2 a. m. and at 9 a. m. the patient received calcium lactate by the aid of the stomach tube, but this treatment did not seem to influence the convulsions. Her condition grew worse, and at noon 4 gm. of calcium lactate in 100 cc. salt solution were introduced into the arm vein. There were no further convulsions, but the patient's condition rapidly grew worse, and at 2 p. m. she died.

Autopsy (No. 3072), 3 p. m.

Anatomical Diagnosis.—Generalized tuberculosis; tuberculous bronchial lymphadenitis; tuberculous meningitis; acute tuberculous bronchopneumonia with cavity formation; chronic tuberculous pleuritis (bilateral); tuberculous pelvic peritonitis; chronic perihepatitis and perisplenitis; miliary tuberculosis of the liver; fatty degeneration of liver; chronic splenic tumor; ovarian cysts (bilateral); anæmia; emaciation.

Brain: The dura is closely attached to the pia arachnoid membranes over the convexity of the right hemisphere. There is a considerable amount of œdema in the pia arachnoid membranes. Both temporal lobes are closely bound down to the inferior portion of the parietal lobe by rather firm adhesions; when these are broken the surface between these two lobes is seen to be considerably roughened and of a pinkish gray color. Scattered over the surface one sees small, transparent nodules, most of which are quite small, pinhead in size. Along the vessels in this region numerous similar nodules can be made out. A similar granulation with small, opaque, grayish nodules is found over the base of the cerebellum and on both sides of the medulla. Even over the convexity of the brain one finds here and there small nodules. Numerous sections through the substance of the brain fail to reveal anything abnormal.

CASE II.—S. H., colored female, age 26 years, was admitted to the medical clinic of the Johns Hopkins Hospital, on February 7, 1909, complaining of headache. Her history was unimportant from the standpoint of her present illness. This began about three weeks prior to admission with headaches. These were accompanied by epistaxis.

Physical examination on admission: The patient was very restless, moving from side to side in bed; although rational in the morning, she did not answer questions or notice anything about her at 4 p. m. of the same day. There was a distinct exophthalmos and an internal strabismus. Passive flexion of the head was resisted, and the body could be raised with the hand under the occiput. The patient complained during the manipulations. The glands of the axillæ and of the neck were somewhat enlarged. Thorax was symmetrical. The heart and lungs revealed nothing of note. The abdomen was flat, and there was no tenderness, but a slight voluntary resistance. There was an atypical Kernig's sign present.

On the evening of February 7 the patient suddenly had a convulsion. This was general in character, involving the entire body. During the next hour she had six similar convulsions. The last two were observed and were described as follows: Long inspiratory cry followed by tonic convulsions, which first involved the muscles of the face and eyelids. The arms became involved, and the hands assumed the typical obstetrical position observed in tetany. The body was in opisthotonos, the head retracted and the back arched. The legs were much less involved than the arms. The patient had two slight convulsions on the morning of the 8th.

The rigidity of the back had increased markedly, and the patient's condition gradually grew worse, though there were no more convulsions. Fluid obtained by lumbar puncture on admission showed many mononuclear cells, and a few slightly beaded acid fast bacilli.

Autopsy (No. 3170), February 11, 3 p. m.

Anatomical Diagnosis.—Tuberculosis of the retroperitoneal and mesenteric lymph glands; tuberculosis of the thoracic duct; tuberculous endocarditis; general miliary tuberculosis; tuberculous meningitis; tuberculosis of lungs and pleura; miliary and conglomerate tubercles in the liver, spleen, and kidneys; anæmia; tuberculosis of the parathyroid.

Brain is rather dry. The surface is congested slightly, and one sees scattered over the convexity of the brain, even as far as the median line, numerous small, semi-transparent, grayish, opaque nodules, which are only 1 or 2 mm. in diameter. The Sylvian fissures are obliterated by rather firm adhesions, and when these are separated one finds a granulation tissue in this area. Along the blood vessels one can see numerous tubercle-like nodules. Over the base of the brain, especially the pons, there is an exudate which is firm. In this one can make out a few small nodules. The cerebellum does not show any of these tubercle-like nodules—nor does one see any on the base of the occipital lobe.

Parathyroids: Four parathyroids were found. They were somewhat enlarged, but this was not sufficient to be worthy of note. Serial sections were made of the glands, and a conglomerate tubercle, involving approximately the lower third of one of the glands, was found. This had a definite caseous center and was surrounded by a dense zone of epithelioid and mononuclear cells. Numerous typical giant cells were found in this zone. Otherwise the parathyroid glands seemed normal.

Briefly to summarize: Both patients were colored females, aged 21 and 26 years respectively. The illness was acute, and in both cases typical symptoms of tetany had been observed during life. At autopsy both showed general miliary tuberculosis. In one of the cases there was a small focus of tuberculosis in one parathyroid gland.

It is greatly to be regretted that the parathyroids were not carefully examined in the first case, but it is interesting to note that the convulsions immediately subsided following the injection of calcium into the arm vein.

It will be remembered that MacCallum and Voegtlin have recently shown that there is a very intimate connection between the calcium metabolism and the parathyroid glandules. They found an increase in the calcium output in the urine and feces with a diminution in the blood and brain of animals suffering with tetany. More important than this, however, they found that the symptoms of tetany could be entirely relieved by injection of calcium.

With this work in mind, it is quite natural that we should turn first of all to the mineral metabolism in tuberculosis for a possible explanation of the symptoms of tetany in this disease.

Interest in the calcium metabolism of phthisical individuals was aroused long ago, especially in France, by the work of Gläube, who showed that the calcium of the urine was increased in tuberculosis. Senator came to the same conclusions. These authors thought an excessive excretion of calcium occurred in incipient tuberculosis. But as Ott points out, these observations are only of limited value, since the above mentioned observers, like many others, did not take into consideration the mineral value of the ingested food nor the possible dissipation of these substances through the feces and sputum. Ott reports a number of cases of tuberculosis in which he analyzed both the ingested food and the excreta, including urine, feces and sputum. In his first series he includes five cases of outspoken pulmonary tuberculosis. In none of these was there a body loss of calcium, and in the majority there was a slight retention, which the author is inclined to ascribe to variations in the rapidity with which calcium is excreted. In his second series Ott includes three cases; in two of these his results were similar to those obtained in the first series. But in the third case, despite the fact that the individual was in nitrogenous equilibrium, there was a marked loss of mineral substances and of these the calcium was most prominent. The author concluded that demineralization in advanced tuberculosis must be conceded, but that this is not a constant finding.

Of course, these cases are by far too meagre to allow of any positive conclusions, but they are certainly inspiring for further work. It seems quite possible that in certain cases of tuberculosis there may be a marked disturbance in the calcium metabolism. This might be of sufficient extent alone to bring about a deficit in the calcium of the circulating fluids, and in this way cause an hyperexcitability of the nerve cells. This is at least a tempting hypothesis which would explain tetany in some cases of tuberculosis, where no lesion of the parathyroids is demonstrable. On the other hand, if there is already a deficit of calcium in the circulating fluids of the body, a slight injury to the parathyroids might very readily be of crucial importance and cause sufficient additional disturbance in the calcium metabolism to bring about tetany.

I wish to take this opportunity to thank Dr. L. F. Barker and Dr. W. S. Thayer, who so kindly allowed me the use of the medical histories.

Conclusions.

1. Tetany may occur in advanced tuberculosis.

2. This may be associated with tuberculosis of the parathyroid, but the lesions in these glandules in the cases so far reported are not extensive enough to account for the symptoms.

3. In some cases of advanced tuberculosis there is a disturbance in the calcium metabolism of the body, with namely an excessive excretion of this mineral.

4. This may in itself be sufficient to bring about a condition of hyperexcitability of the nerve cells, and the presence of even a slight lesion in the parathyroid glands may be sufficient to cause tetany.

5. Calcium salts should be used therapeutically in tetany complicating tuberculosis.

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THE USE OF ANIMAL MEMBRANE IN PRODUCING MOBILITY IN ANKYLOSED JOINTS.[1]

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The production of mobility in ankylosed joints—whatever the character of the ankylosis—is a problem which has interested surgeons, and particularly the orthopedic surgeon, for a long time. Formerly we were content to rid our patients of their diseases and to obtain a joint which was serviceable for the work put upon it. With our increased knowledge of bone pathology and with the light that the Roentgen ray has shed on affections of bones and joints, surgeons for the past ten years have attempted not only to cure the diseased part, but to restore the part so that it could perform as nearly as possible all its normal functions.

It is a common saying that "Necessity is the Mother of Invention." It might as truly be said that necessity is the mother of joint surgery which has for its object the production of mobility. Through this necessity the earliest work which was done along this line was the attempt to produce mobility in those cases of ankylosis of the joint where the metabolism of the body was greatly interfered with owing to that ankylosis.

In 1893 Helferich excised the condyle of the inferior maxillary bone in a child one year of age, and inserted an attenuated flap from the temporal muscle. This was repeated by Lentz, Henle, and others. Instead of a flap from the temporal muscle a flap from the masseter was used by Mikulicz in 1895. Both the coronoid process and the condyle of the inferior maxilla were removed and a flap of the temporal muscle inserted by Bilezguski and Hoffa, while Kusnetzow used a masseter flap in the same operation. The superior portion of the entire ramus was removed by Rochet and Schmidt, and a flap from the masseter was interposed. Gluck in 1902 used a skin flap in place of the muscle flap of earlier surgeons. Not only have flaps been used by various surgeons, but foreign materials have been inserted between the articular surfaces to produce motion in ankylosis of the joint. In 1901 Orlow inserted metal plates and also gold foil to relieve this condition. All of these operations have met with greater or less success.

Following closely upon the operations for ankylosis of the joint where nature demanded mobility to carry on the processes of life, surgeons began to operate upon other ankylosed joints, chiefly the knee, hip, and elbow, in which, while mobility was not a necessity, it was greatly to be desired.

The materials used between the articulating surfaces of a joint have been numerous. A muscle flap from a muscle contiguous to the joint has been preferred by most surgeons. The muscle flap was used by Quenn, Albarran, Nelaton, Delbet, Murphy, Hoffa, Schantz, and others in ankylosis of the elbow joint; Rochet, Nelaton, Hoffa, and others in ankylosis of the hip and leg, others in the knee. This has given a marked improvement in the hands of some men, while it has been unsatisfactory with others.

Murphy has urged the use of a flap of fascia covered with a good layer of fat, and reports some remarkable results. He concludes that the results depend upon the formation of a bursa. Chlumsky, disappointed with the results of muscle flaps, used non-absorbable materials of zinc, rubber, celluloid, silver, and layers of celloidin, but no permanent results were obtained. He substituted for the non-absorbable materials he had used absorbable plates of decalcified bone, ivory, and magnesium. These results, while better than those with non-absorbable materials, were not on the whole satisfactory. R. T. Weglowski, in the *Centralblatt für Chirurgie*, April 27, 1907, reports a case in which he trans-planted the cartilage from the seventh rib into the ankylosed elbow joint, and obtained from 60 to 70 degrees of motion after five weeks.

There are certain reasons why the interposition of muscle or fascia or any non-absorbable material into a joint cannot form the ideal method for the production of mobility. The anatomical structure of the joint is often materially interfered with when any bulky substance sufficient to cover the entire joint, as a muscle, in interposed. It necessitates too large an excision of bone, and on the other hand if too little muscle or fat is interposed, ankylosis results. In a majority of cases the interposition of a living tissue is followed by a constant pain, due to pressure upon its nerve endings. While we may attain a certain degree of motion by the interposition of muscle or fascia, the motion is generally unnatural in character and quite often results in an unstable joint.

With these objections before me I undertook to find an absorbable material which was thin and pliable enough to allow of easy adjustment within the joint, and which would remain there beyond the period of new bone or fibrous formation. This is simply a preliminary report. The experimental study upon animals and the pathological changes which are formed with the use of the animal membrane in various types of inflammation, and further operative results, are now being carried on.

The membrane which I have used is from the pig's bladder, and chromicized so as to remain intact about 40 days. I am greatly indebted to Messrs. Johnson and Johnson, who have spent much time and labor in finding a membrane of the proper thickness and pliability, and chromicizing it to the proper degree.

CASE 1.—L., white, male, age 21 years, was admitted to the hospital April 28, 1908.

The boy had an acute attack of gonorrheal arthritis in the knee. He was in bed for 8 weeks following this attack, and afterwards found that his knee was perfectly stiff in a position of flexion of 15 degrees. He was admitted to the hospital in the

[1] Read before the American Orthopedic Association, Hartford, Conn., June 15, 1909.

hope of producing motion in this ankylosed joint. The X-ray picture showed complete bony ankylosis between the patella and the femur and between the femur and tibia, with a new production of bone posterior to the condyle. An arthrotomy was performed April 28, 1908. Two lateral incisions were made along the sides of the patella, and the joint was found to be completely ankylosed by new bone formation. The patella was chiseled from the femur and also the tibia from the femur. After a great deal of difficulty complete mobility was obtained and the new bone formation was removed. All evidences of the cartilage had been obliterated and the synovial membrane also had disappeared. Cargile membrane was inserted into the joint so as to completely prevent contact of one raw surface with another, the membrane being sewed into the joint by means of catgut sutures. During the operation, in order to get the joint perfectly movable, the tibial tubercle was broken away from its attachment. The wound was closed entirely, the leg being put up in a cast; the tubercle was fixed in place. There was a rise of temperature for 3 days following the operation, but after that the temperature remained normal. On the 8th day the cast was removed and passive motions instituted. At the end of 30 days, however, the motion was only 10 degrees, and this has persisted for 13 months since the operation.

Synopsis: Boy aged 21 years. Gonorrheal arthritis. Duration one year. Complete bony ankylosis. Insertion of Cargile membrane. Motion of 10 degrees only, after 13 months.

Case 2.—B., white, female, age 50 years, was admitted to the hospital July 16, 1908.

The duration of her disease had been 1 year and 3 months. The left knee is swollen and absolutely rigid. The infectious process is apparently a septic one, coming from an infection of the tonsils. The X-ray picture shows bony ankylosis between the patella and femur and between the tibia and fibula. An arthrotomy was performed on July 16, 1908, lateral incisions being made on both sides of the knee. The bone was chiseled through beneath the patella and between the femur and tibia, and Cargile membrane was inserted between the ends of the bone and sewed in place by means of catgut sutures. There was a slight rise of temperature for 3 days following the operation, and then it subsided to normal. The leg was put up in a cast and dressed on the 10th day, when the wound had healed *per primam*. There were about 15 degrees of flexion at that dressing. Passive motions were instituted, but the knee remained absolutely stiff 3 weeks after the operation. The patient has continued fairly well, walking on her leg but without any motion.

Synopsis: Septic arthritis of the left knee. Insertion of Cargile membrane. Recovery without motion.

Case 3.—J., white, male, age 6 years, was admitted to the hospital October 28, 1907.

The patient has tuberculous arthritis of the knee and of the tendon sheath of the wrist. Duration of the disease has been 3 years. The knee is slightly flexed at 20 degrees and there is a subluxation backward of the tibia. There is no sinus. The knee is swollen but without rise of local temperature. The X-ray picture shows an erosion of both condyles of the femur. There is no motion in the joint, but the X-ray picture would indicate that this ankylosis is a fibrous one. On April 28, 1908, an arthrotomy was performed by making lateral incisions on both sides of the knee. Fibrous ankylosis was found to be present between the patella and the femur and between the tibia and the femur. These adhesions were broken up by means of a periosteal elevator, but the disease did not look absolutely quiescent. The ordinary Cargile membrane was inserted between the ends of the bones and beneath the patella, and held in place by catgut sutures. The wound was closed without drainage and the leg put up in a plaster spica. There was a slight rise of temperature, going up to 102° F. the day after the operation, and continuing slightly elevated for 4 weeks. The first dressing was made on May 6, 1908, 8 days after the operation, and the wound was healed *per primam*. On May 15, 17 days after the operation, there was a small sinus formed at the end of the wound and the remains of the Cargile membrane was sloughed out with a slight amount of tuberculous pus. This sinus continued to remain open for 3 months after the operation, when it finally healed.

Synopsis: Boy aged 6. Tuberculosis of the knee and tendon sheath of the wrist. Insertion of Cargile membrane into the knee for mobility, with the result of starting up the tuberculous process. A stiff knee resulted, but in better position, 3 months after operation.

Case 4.—S., white, male, age 6½ years, was admitted to the Johns Hopkins Hospital, in the service of Dr. W. S. Halsted, October 8, 1908.

The duration of his disease had been 4 years. The boy has tuberculosis of both hip joints with complete ankylosis in each one. He had been treated at other hospitals by means of extension and later by plaster spicas. On admission he was a rather emaciated little boy with his hips in the following position: right thigh is flexed at 25 degrees and left at 35, the left thigh is abducted 35 degrees and right thigh is adducted 35. There is absolutely no motion in either joint. There has been no sinus present, and the disease is apparently quiescent. Owing to the fact that both hips were absolutely immovable it was thought best to attempt to obtain motion in the right or adducted hip. The X-ray picture taken before the operation shows marked destruction of the head with a proliferation of new bone. On October 12, 1908, an arthrotomy of the right hip was performed, the joint being opened by means of an anterior incision. The capsule, which was thickened, was closely adherent to the bone. Any attempt to produce motion of the hip caused motion in the epiphyseal line, the epiphysis itself being tightly adherent to the pelvis. The head was separated from the acetabulum cavity and the acetabulum curetted, making as smooth a surface as possible. A membrane of chromicized pig's bladder was placed between the head and the socket and bound tightly about the neck, where it was sewed with catgut sutures. The wound was closed and the leg put up in plaster in a position of abduction of 20 degrees. The first dressing was made 8 days after the operation. Healing had taken place *per primam*. A plaster trough was left in which the leg should be kept in a position of abduction of 15 degrees, and passive motions were begun. On December 12, 2 months after the operation, the boy is able to get about, and there was a voluntary possible flexion of 35 degrees, abduction 15, adduction 10, and possible rotation of 25 degrees.

A letter received from the boy's father 1 month ago, i. e., 7 months after his operation, says the child is getting about very much better and can bend his leg nearly to a right angle. He says that he does not suffer any pain.

Synopsis: Tuberculous arthritis of both hips. Duration 4 years. Both hips ankylosed. Insertion of animal membrane with a gain in flexion of 35 degrees and corresponding gain in abduction and adduction, 2 months after operation, and report of possible flexion to a right angle, by his father, 8 months after operation.

Case 5.—R., age 4½ years, was admitted to the hospital November 7, 1908.

This child was born with a congenital synostosis between the head of the radius and the ulna. There is no ability to supinate the arm at all, and the dorsum of the hand points directly forward. Motions of flexion and extension at the joint are normal. X-ray plate shows the ankylosis of the bones together with a marked curvature of the radius, as it has been held continually in extreme pronation since birth. In all other respects the child is perfectly normal.

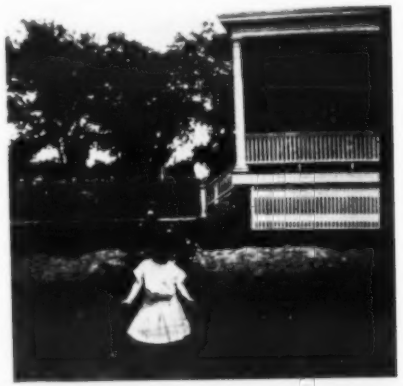
Operation for relief of the synostosis was performed November

CASE 1[1].—Radiograph. Gonorrheal arthritis of knee. Before operation.

CASE 1[2].—Radiograph. Gonorrheal arthritis of knee. Three months after insertion of Cargile membrane.

CASE 1[3].—Photograph. Gonorrheal arthritis of knee. Possible flexion 15 months after use of Cargile membrane.

CASE 4.—Radiograph. Tuberculosis of hip—double. Before operation.



CASE 5.—Photograph shows possible supination of forearm. 100 days after operation.

CASE 5[1].—Radiograph showing synostosis of radius and ulna before operation.

CASE 5[2].—Radiograph of radius and ulna, 3 months after operation.

CASE 6[1].—Radiograph 6 months after operation with insertion of animal membrane. Tuberculosis of knee.

CASE 6[2].—Photograph showing possible flexion 6 months after operation. Tuberculosis of knee.

CASE 8.—Photograph. Possible reflexion, 40 days after operation.

CASE 8[1].—Radiograph of knee before operation, showing bony ankylosis. Gonorrheal arthritis.

CASE 8[2].—Showing possible flexion 40 days after operation. Gonorrheal arthritis.

10, 1908. Incision was made over the outer aspect of the forearm below the olecranon, exposing the upper end of the radius and ulna. The periosteum enclosed these two bones as if in a sheath. This was separated by means of the chisel, and the bony ankylosis was removed. Supination was then allowed so that the hand turned about 100 degrees. One could get no further on account of the curvature of the radius. Cargile membrane was placed between the ends of the bones. The wound was closed and the arm put up in plaster with the arm in a position of supination of 100 degrees. The temperature rose after the operation until it reached 102° F. on the following day, and remained slightly elevated for 10 days after the operation. Massage was commenced on the 8th day following the operation and was continued for some time, but ankylosis reoccurred in about 30 days following the operation. The membrane here used was the ordinary Cargile membrane.

On February 25, 1909, the patient was readmitted to the hospital and operated upon the following day. The synostosis was found to have reformed and bony ankylosis to have taken place. Chromicized pig's bladder was inserted between the ends of the bone as in the former operations, and the arm put up in supination of 100 degrees. A slight temperature reaction took place, which persisted for 10 days after the operation. Massage has been kept up since 8 days after the operation. To-day, 100 days after the operation, supination is possible up to 100 degrees, but the arm as yet can go no further owing to the twist in the radius. A brace is being used in the attempt to bend the radius into its proper position. If it were not for the fact of the curving of the radius it is quite possible that supination would be entirely normal.

Synopsis: Child 4½ years. Congenital synostosis of radius and ulna. Mobility of 110 degrees produced by introduction of chromicized pig's bladder.

CASE 6.—B., white, female, age 14 years, was admitted to the Johns Hopkins Hospital, in the service of Dr. W. S. Halsted, December 10, 1908.

Child has tuberculosis of the knee. Duration of disease 10 years. For the last 3 years the knee has been perfectly well so far as any active process was concerned, and she has been walking on it with flexion of 10 degrees but absolutely no mobility. The patella is tacked down firmly to the top of the femur, and there is fibrous ankylosis between the head of the tibia and the femur. An operation was performed to produce motion. Lateral incisions were made on both sides of the knee, and complete fibrous ankylosis was found between the patella and the femur and between the femur and the tibia. This was separated by means of a periosteal elevator and passive motions made until the normal amount of motion was obtained. Chromicized pig's bladder was inserted between the patella and the femur and between the femur and tibia so that the raw surfaces were completely shut off. The membrane was sewed in place by means of catgut sutures and the wound closed. A plaster dressing was put on the leg while the leg was in full extension. For 3 days following the operation there was a slight rise of temperature to 101° F., but after that time it remained normal. On the 8th day the plaster was removed and passive motions instituted. The child was allowed to walk at the end of 3 weeks. To-day, 6 months after the operation, the condition is as follows: The leg can be brought into full extension and can be flexed at 75 degrees. There is no pain on motion, and the child walks with a slight limp which is due to a shortness of the leg from her early tuberculosis.

Synopsis: Girl 14 years of age. Tuberculosis of the knee of 10 years duration, with complete fibrous ankylosis. Arthrotomy and insertion of animal membrane and recovery of function of 75 degrees.

CASE 7.—L., white, female, age 16 years, was admitted to the hospital December 28, 1908.

This is a case of tuberculosis of both hips and also tuberculosis of the sacrum for the past 6 years. Right leg is in a position of flexion of 95 degrees, adduction 75 degrees. It lies entirely across the body and is rotated inward 20 degrees. The scar of an old sinus is seen 15 cm. below the trochanter. There is complete bony ankylosis at the hip joint. An X-ray picture shows marked destruction of the head and new bone formation about the hip joint with coxa vera. The left leg is flexed at 110 degrees, abduction 20, external rotation 10 degrees. Hip is almost completely ankylosed, and radiograph shows marked bony destruction at the hip joint. When the patient attempts to walk she assumes a squatting position, feet, buttocks, and hands resting on the floor. There is a discharging sinus along the left side of the rectum; a bismuth injection and an X-ray plate show that the starting point is in the left side of the sacrum. Operation was performed on the left hip on December 30, 1908. A Hoffa-Lorenz incision was made over the right hip joint, and the head of the bone was separated from the acetabulum cavity by chiseling through the new bone formation. The cartilage of the hip had been almost completely destroyed, as well as that of the acetabular cavity. All the adductor muscles were divided by the open method, and the leg was then brought down from its position to 90 degrees flexion and 20 adduction, so that it lay perfectly flat and was in 15 degrees of abduction. Chromicized membrane from pig's bladder was inserted between the head and the acetabulum cavity and secured about the neck so that the head was completely covered by means of catgut sutures. The wound was closed and healed *per primam* within 10 days. At that time massage and passive motion were instituted and kept up for the following 6 weeks. At the present time the leg is lying flat on the bed, there is voluntary flexion of 50 degrees, abduction of 30, and adduction of 10. The hip is not painful and the patient can bear her weight upon it without discomfort. She has not progressed so rapidly as she would have done, owing to the fact that we have been trying to keep her quiet on her back so as to heal up the focus in the sacrum by means of bismuth injections, which so far have failed.

Synopsis: Girl with tuberculosis of the right hip. Duration 6 years. Complete bony ankylosis and deformity of 90 degrees flexion, 20 adduction, and 15 of internal rotation, and now has motion to the extent of 50 flexion, 30 abduction, 10 adduction, and good rotation in and out, 156 days after operation.

CASE 8.—S., white, male, age 20 years, was admitted to the hospital April 18, 1909.

Patient has complete bony ankylosis of left hip and left knee joint. He was taken suddenly with acute rheumatism which settled in the hip and knee 3 years ago. The inflammatory condition remained in each joint for 3 months. Patient was in bed for 9 months. The onset of this condition of the joints was preceded by gonorrhea 2 weeks before. On admission the left leg was held in a position of abduction of 15 degrees and of flexion of 15 degrees. It was not tender but was absolutely immovable. The X-ray picture shows entire destruction of the head and the acetabulum cavity with new bony ankylosis. The knee is flexed about 10 degrees; the patella is immovable, and not the slightest motion is to be obtained between the femur and the tibia. The X-ray picture of the knee shows entire destruction of the joint surfaces with bony ankylosis between the patella and femur as well as between the tibia and femur, with the formation of bone behind the condyles and in front of the articulation of the femur and tibia. The boy was absolutely incapacitated owing to the ankylosis of both hip and knee joint on the same side, and it was deemed best to attempt to obtain motion of his knee joint at this time. On April 20, 1909, an arthrotomy was performed on the left knee. A perpendicular incision was made on either side of the knee joint, and complete bony ankylosis was found between the patella and femur and the femur and tibia. One was unable to separate these by a periosteal elevator, and they had to be cut through by means

of a chisel. After a good deal of difficulty this was accomplished, separation at the line of the articulation was made, and the new bone formation in front of and behind the condyle was chiseled away. Chromicized pig's bladder was inserted, one piece between the femur and tibia, and another piece between the patella and femur, until the entire joint was covered. These were sewed in place by means of catgut sutures at the reflexion of what should have been synovial membrane. The wound was closed and the leg put up in plaster in full extension. The day following the operation the temperature rose to 101° F., but reached normal again in 8 days. On the 10th day the cast was removed and the wound had healed *per primam*, and passive motions were begun. The boy left the hospital on May 30. In 41 days after the operation he was walking with the aid of a cane and bearing his weight on his leg. At this time the patella was freely movable, passively and actively. He has the ability to move his knee 35 degrees, and the possible flexion and extension have been increasing daily.

Synopsis: Gonorrheal arthritis in a boy of 20, with complete ankylosis of the knee and hip for 3 years. An arthrotomy of the left knee with substitution of animal membrane was performed, with the result of 35 degrees of active flexion 40 days after operation.

As has been said, this paper is presented to point out the methods used rather than to draw any definite conclusions. The small number of cases and the short space of time since the first operation (one year and a half) prevent us from making too definite statements. It seems, however, that certain suggestions offer themselves, from a study of the cases, which it is worth while to consider.

A definite amount of permanent mobility has been obtained by the insertion of chromicized pig's bladder into a joint, provided the membrane can be retained intact for a period of 30 to 40 days. In Cases 1, 2, and 3, where simple Cargile membrane was used, no permanent motion was obtained owing to the fact that the Cargile membrane is absorbed in a period of 10 to 15 days. In Cases 4, 5, 6, 7, and 8, where the chromicized pig's bladder was used, a membrane which remains at least for 30 days, a permanent amount of motion resulted in each case. Case 4, tuberculosis of hip, gave 35 degrees of flexion after 8 months; Case 5, synostosis of elbow, gave 110 degrees of motion after 3 months; Case 6, tuberculosis of the knee, gave 75 degrees of motion after 6 months; Case 7, tuberculosis of the hip, gave 50 degrees of motion after 5 months; and Case 8, gonorrheal arthritis of the hip, gave 35 degrees of motion after 40 days. In each case the amount of motion has been permanent and of definite utility. Passive and active motions, together with massage, have been instituted immediately after the first dressing, *i. e.*, not later than the 10th day, and continued daily. This is essential in the production of motion and should be insisted upon notwithstanding the discomfort, for in every case the muscles are so atrophied from disuse that it is necessary to stimulate them into action.

The amount of motion stated in these cases is active and not passive. In the limits of active motion the joint motion has been free of pain, in each case. The joint as far as possible has been restored to its normal state, and there is no bulky foreign material to cause discomfort by its presence.

The character of the motion has been as normal as the anatomical changes in the shape of the bone will permit. There is an absence of the wabbling which is seen in cases where a muscle or fascia flap is inserted between the bones. In hip joint cases the deformed head of the bone fits closely in the socket, and there is an absence of that waddling congenital hip-like motion.

Our cases have shown a post-operative rise of temperature which persisted from 3 to 10 days, but suppuration has not taken place except in Case 3, where a tuberculous discharge was set up. This was a case of tuberculosis of the knee with fibrous ankylosis. Our enthusiasm led us to operate before the process was entirely quiescent, and, while no harm was done, no good was accomplished. One should be sure in all ankyloses from tuberculosis that the disease has been entirely quiescent for quite a long period before attempting operation. In Cases 4, 6, and 7, tuberculosis of the hip and knee, where all signs of the infection had been dormant for over a year or more, no trouble was encountered, and they gave gratifying results.

The joints operated upon in this series have been the hip, knee, and elbow. They all lend themselves readily to the insertion of the membrane. The best incision for an arthrotomy of the knee has been found to be a lateral incision on either side of the patella, while the anterior incision from the anterior superior spine gives us the best exposure in cases of ankylosis of the hip.

The entire success of the operation depends upon the character of the membrane used. In the first place it should be absorbable. Secondly, it should remain intact from 30 to 40 days. Thirdly, it should be pliable enough to be adapted to the contour of the joint. Every raw surface should be absolutely separated by it from that with which it would normally come in contact. The membrane should have body enough to prevent its tearing, and it should be firmly held in position by absorbable sutures.

Our results of permanent motion attained by the use of chromicized pig's bladder in ankylosed joints have been such as to make a more exhaustive study of the method advisable.

THE MUNICIPAL MANAGEMENT OF TUBERCULOSIS.

By Wm. Charles White, M. D., Pittsburg, Pa.

On going over what I have to say to you on the subject of municipal management of tuberculosis, there arose in my mind the closing sentence in one of the paragraphs of Walter Bagehot's essay on Hartley Coleridge, which runs as follows: "If we are to be dull, surely we will be dull in silence. Do not sermons exist, and are they not a warning to mankind?" The serious phase of the tuberculosis problem which I wish to present partakes a good deal of the nature of a sermon, yet I trust that our experience may contain a lesson or two for some of my hearers.

The tuberculosis question in any municipality has two definite problems to be solved; first, the medical problem; and second, the sociological problem, which invades every portion of the social fabric of our country.

The medical side is, of course, a most important factor, involving, as it does, such problems as pointing the way, making early diagnoses, the care of the already sick, and the search of the still elusive specific cure.

The medical profession, while it does wonders through many of its members, yet constitutes in itself one of the most serious problems of the sociological side of the tuberculosis situation. A large proportion of the profession are still ignorant of the fundamentals underlying our present conception of tuberculosis as a disease and the cure of the same. Many years must pass before the difficulty is eradicated by the production of more careful doctors through better teaching in our schools.

While this is true, there is much criticism fairly offered by the majority of the profession on that increasing group of medical men, the tuberculosis experts. So often these are men who know little else of medicine than tuberculosis, and who spend much time in criticism and abetting criticism of the woeful lack of knowledge of that potent group, the general practitioners. Oftentimes the only recommendations many of the experts have is that they have had tuberculosis themselves and have in consequence studied this one disease carefully. Too many specialists to-day are experts in picking out a small tuberculous focus rather than experts in tuberculosis.

In studying certain discrepancies in statistical life problems, which appeared when the time reckoned was only that from birth to death, Pearson made the interesting discovery that the discrepancies disappeared completely when the nine months between conception and birth were taken into account. So with the above discrepancies many of them will disappear when we take into account the time before the birth of the doctor, and establish some better method of teaching this disease which in its clinical aspect to-day is looked upon still as one which every doctor knows about without teaching.

In this doctor's pre-natal period some of the mistakes are so gross as to be unpardonable. The hospital where he is taught admits no tuberculous cases. In spite of this law tuberculous cases are entered for operation, from mistaken diagnoses, for child-birth, through influence, etc., and the ordinary precautions of prevention and cure are neglected. Consequently the embryo doctor is untaught; but infinitely worse, the very place which should be a model for education in this line becomes a source of great danger of infection to those whose duty calls them there. Ask yourselves of the hospitals of your own knowledge and of the doctors and nurses that have fallen during their course. How many hospitals use burnable closed sputum cups in place of porcelain ones, on which the sputum dries and scatters and flies gather? Do not influenza, pneumonia, typhoid fever, and other sicknesses spread in like manner from the sputum?

How much better it would be for hospitals to-day to say, we take tuberculous cases, teach our doctors, students, and nurses carefully about it, use every precaution for prevention and cure. If this were done there would not be to-day the long list of sick placed on the debit side of our carelessness account, the tremendous fear of the sickness, and the ignorance of preventive measures.

One word more. The difficulty of finding to-day a nurse who knows anything about tuberculosis, and who is not afraid of it, save one of the group who have suffered from it, must have struck most of you. No wonder, when the above condition exists in our hospitals. About all we do in the hospitals in regard to a nurse's relation to tuberculosis is to neglect to guard her against infection with tuberculosis.

The Tuberculosis League of Pittsburg has attempted to help these difficulties by arranging to furnish the larger hospitals with burnable cups, and by establishing an extension course for nurses in the Tuberculosis Hospital, which it now carries on with the Western Pennsylvania Hospital and the Homeopathic Hospital, giving each nurse two months' training in tuberculosis nursing and district work. The educational result from this connection your imagination will supply both for the hospitals and homes of the municipality.

The sociological problem, however, is the broader field and envelops much of the above tuberculosis work to-day. There are three groups actively interested: The State, the health authorities of the municipality, and charitable organizations. There is, of course, work for all. The greatest difficulty at present is to establish some correlation or centralization of work which will prevent waste of energy.

It is the State's duty to look after the work in those parts of the State having no other health control, and to help those municipalities from which she demands the care of their own public health without, however, dissipating the work of the municipality.

In the municipality which is large enough to be entrusted with its own public health government, the work should undoubtedly be centralized in the department of health of the city. The care of the city's poor consumptives should be provided for by public taxation.

The charitable and private organizations have double duty:

1st. They must educate the inhabitants of the municipality to the point of accepting and carrying out this duty.

2d. They must provide for the great body of unfortunate consumptives who are not wholly destitute.

Let me repeat again that the removal of this scourge is a matter of public health, and that all labor that is done should be with the ultimate intention of centralizing the work with some permanent policy in the municipal department of public health. Here should be a record of every case in the city, its source and danger of infection, and the assurance of its proper care by public or private measures.

Most of the active work to-day emanates from private charitable sources, and the accomplishments of these, as well as their mistakes, may well be reckoned with as part of the arma-

ment of the municipality when the work is finally safely lodged in its hands.

In the foremost rank stands the educational work. This to be effective must be placed upon the same basis of repetition and continued effort that marks the value of all other useful educational work; it must have for its object a fully educated community in which no one has escaped the gospel. Reiteration must be its bulwark. I have little faith in spasmodic and grand-stand work—such as the graphophone and the brass band. The effect is not lasting nor are the results permanent. I fear the special lecture to adults is in part open to the objection also that the effort is spasmodic and the audience past the impressionable age.

It would seem of more value to utilize continuously as with other educational work the permanent educational gatherings, the school and the church, with a permanent exhibit in some public building where people gather constantly, which exhibit would teach in a graphic way, with few words, the way to care for a consumptive at home, and the laws governing the prevention and cure of this disease.

With this conception of the work, the Tuberculosis League two years ago made the effort to establish in the schools of Pittsburg some definite systematic course of study that could be continued year after year, and eventually result in a saturated community. After much personal labor they obtained a concession which allowed them to put a nurse, Miss B. Stark, who was admirably fitted for the work, in charge of the task. Miss Stark developed the field admirably, and has made the teaching acceptable to children, teachers, school management and homes. Her work consists in talks to teachers, talks to children, talks to mothers, exhibits in school halls, and simple pamphlets sent with the children to the homes with the urgent request that in the home they tell what they have heard. We believe that the phrase "a little child shall lead them" may contain the solution of many of the problems contained in Miss LaMotte's interesting and distressing study.

Hospitals.

We miss by half the value of hospitals for consumptives by moving them so far away from the town. I do not mean that at times the country is not much better than the town, but that it is not enough better to counteract the influence on the town itself. I know of no more potent educational factor in tuberculosis work to-day than the existence, in the midst of the city, of a hospital of wide porches and shacks filled with beds in which tuberculous patients recover. A spot can usually be chosen which has open space around, and I am convinced of this, that when we realize that tuberculosis is a malady that must be treated as carefully, individually and collectively, as typhoid fever and pneumonia, we will be able to cure as well in such places in town as in the country.

A hospital in such a place helps to overcome the fear which has resulted from our modern methods, helps to teach the friends of patients how to do the trick, by rapid turning over of patients accomplishes wonders in individual education of the consumptive, and beyond all, stimulates the municipality to the belief that it is an economic problem which will result in money saving for it to care for its own consumptives, and to have the money expended in such care spent in its own market. Let me repeat again for the municipality, the question of tuberculosis is a public and private municipal business.

Nothing perhaps is more common to-day in tuberculosis work than the consumptive who has been put in a condition of partial recovery who returns to labor and old home conditions, only to break down, and with lost chances to try to do the whole thing over again. The first cure business is a revelation; the second, often a hardship never completed. This problem, which may be stated as the "problem of conservation of work done," is a very serious one.

Much of the belief of climatic specificity is doubtless due to relapse following long railway journeys and the excitement of home coming.

The conservation of work done I believe can only be accomplished by a carefully correlated system in which the patient is moved from department to department, as the supervision of his case requires more or less attention. A specific example will illustrate: A is found to have active tuberculosis with fever in the dispensary; he is moved to the hospital where with strict care he becomes well enough to move around and start work; he is then moved to the farm and gradually worked back to eight hours of labor a day; he is then moved into the night camp and his regular work; he is then discharged with supervision of dispensary and the dispensary nurse. The night camp, which provides proper facilities, food, and supervision, must, I think, take an active part in this conservation work.

Time will not allow full discussion of the following detail problems which each municipality must meet through its health authorities. The inspection, segregation of cases under proper care and fumigation of orphan asylums, jails, homes, insane hospitals, public hospitals, charitable institutions, etc., but these are for years past the hotbeds of many cases, and need most rigid handling.

The maternity cases, which form a serious difficulty, must be met also. There will be tuberculous maternity cases as long as the world lasts. In the past and at present they do very badly. We have attacked the problem in a small way in Pittsburg, and our evidence is to prove that if mothers be put under good conditions through the later periods of child-carrying, and the birth is hurried through and no nursing allowed, this question is not so serious as has been thought. Of course, vomiting cases and special cases call for special care, but in the main a maternity department of a tuberculosis hospital is bound to be of necessity a powerful adjunct of prevention work.

The open-air school, in conjunction with medical inspection of our school pupils, needs only be mentioned, as you are all familiar with its value.

I belong to those who, for the sake of the 11 per cent of the tuberculous of bovine origin (I believe a much larger percent-

age than this will eventually be proven to have this source), think that merely for the 11 per cent we must, with the utmost severity in every municipality, control our milk, cheese, and butter supplies, and have the assurance that they do not come from tuberculous cows. This is more important than the meat inspection for tuberculosis, I think.

Our struggle must be for an immune race, not for the extermination of every last tubercle bacillus, which is apparently the hope of many. More and more we see the evidence of protection of small doses in healthy resistant bodies. In our municipalities then, our plan must be to get rid of the sources of large doses of tubercle bacilli, and to establish resistant bodies by healthy lives, mainly in our children.

In our endeavors to do what seemed best for the municipality of Pittsburg, the Tuberculosis League, a public charitable organization, prepared and, after much labor, succeeded in having passed a municipal ordinance which should centralize the tuberculosis work in the bureau of health in such a way as to establish a permanency of policy and prevent dissipation of work. The ordinance is as follows:

Creating and establishing in the Bureau of Health under the Department of Public Safety, the Division of Tuberculosis Inspection and Relief, prescribing the powers and duties thereof; how the same shall be controlled and exercised and the number of employees and their salaries.

SEC. I. Be it ordained and enacted by the City of Pittsburg in Select and Common Councils assembled, and it is hereby ordained and enacted by the authority of the same,

That there shall be and is hereby created and established in the Bureau of Health, under the Department of Public Safety, a separate division to be known as the Division of Tuberculosis Inspection and Relief.

SEC. II. That said division shall be under the superintendence and direction of a commission consisting of the Superintendent of the Bureau of Health and four competent and skilled citizens who shall be appointed by the Director of the Department of Public Safety for terms of seven years and serve without remuneration, and which commission shall be designated as the Tuberculosis Commission of Pittsburg. Said commission shall adopt such rules and regulations as they may see fit, not inconsistent with any general law or ordinance, and shall elect one of their number as President and one as Secretary. Vacancies occurring in said commission shall be filled by appointment of the Director of the Department of Public Safety for the full term.

SEC. III. That said commission shall prepare and keep accurate records of all cases of tuberculosis existing in the municipality in such form and detail as said commission shall prescribe, inspect all dwellings, tenements, shops, factories and other places where cases of tuberculosis exist, ascertain the cause of infection and provide for the disinfection and cleansing of the same, and report to the proper department cases needing charitable relief; establish dispensary stations; prepare and disseminate information as to the cause, treatment, and relief of tuberculosis and generally do such work and adopt such measures as will tend to control and eradicate the infection.

SEC. IV. That said division shall have attached thereto one clerk at a salary of one hundred and twenty-five ($125.00) dollars per month, and five trained nurses, clothed with police power, at salaries of seventy-five ($75.00) dollars per month, all of whom shall be appointed by the Director of the Department of Public Safety.

SEC. V. That it shall be the duty of the Director of the Department of Public Safety to provide suitable accommodations in connection with the Bureau of Health for the use and occupancy of said division.

SEC. VI. That any ordinance or part of ordinance conflicting with the provisions of this ordinance be and the same is hereby repealed, so far as the same affects this ordinance.

The nurses, you will see, have police power, the commission is unpaid, and as now appointed has represented on it the State, the city and the tuberculosis charity. It exists for seven years, which insures its policy from interruption. While the State law provides for registration and sequestration of tuberculosis cases dangerous to public health, it must not be thought that this commission can accomplish anything by roughshod methods. It must by gentleness, guidance, and tact steer the way, which it is hoped will eventually result in what is best for the municipality, a tuberculosis management centralized with permanent policy in the Department of Public Health, with a registration there of every case in the municipality, its source and danger, and *the assurance* that it is being properly handled, whether by State, city or charity means.

To-day one of the most serious problems, of course, is the fusion of State and city functions in some way to prevent waste. Personally, I feel that tuberculosis in municipalities entrusted with care of the public health, must be handled by the municipality as a matter of health and charity, with the assistance of the State. The latter, however, must assist in the municipality, and not conduct independent work, which can only lead to dissipation of forces and of money. There is work for all in tremendous amount, but let us be careful that the base and foundation of our work be so firm and broad that it will maintain a superstructure of continuous growth and any size. This, I think, might follow the classification of duties outlined early in this address.

Let me quote as my apology Browning's verse from "Rabbi Ben Ezra":

> Now, who shall arbitrate,
> Ten men love what I hate,
> Shun what I follow, slight what I receive,
> Ten, who in ears and eyes
> Match me; we all surmise,
> They this thing, and I that; whom shall my soul believe?

INDEX TO VOLUMES 1-16 OF BULLETIN.

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CHLOROFORM POISONING. LIVER NECROSIS AND REPAIR.

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There are several important points with which this paper deals and they may be stated briefly as follows: The work of various observers (Howland, Wells, Muskens, and others), together with our own, proves beyond any doubt that chloroform is a powerful poison, that narcosis with this drug for any considerable length of time invariably causes central necrosis of the liver (in animals), and that this necrosis, if extreme, will cause death. Animals vary greatly in their susceptibility to the drug, and a narcosis of short duration may prove fatal or cause but little liver necrosis. It will be shown that chloroform invariably causes a uniformly distributed central liver necrosis, however the blood supply of the lobule may be varied —whether the hepatic artery is ligated or the portal blood excluded from the liver by an Eck fistula. When recovery ensues the repair of this necrosis, which may have involved one-half or more of every liver lobule, is very rapid, and the liver is restored to normal in two or three weeks. This repair is perfect and leaves no scars nor distortion of the lobulation. For the sake of comparison the report of a case of chloroform poisoning in a woman has been added. It will be seen that anæsthesia with chloroform for but 35 minutes caused death four days later, and the autopsy findings correspond exactly with those in dogs, the essential lesion being extreme central liver necrosis (Figs. 1 and 12).

A general discussion and review of the literature is not called for, as there have been several excellent papers during the present year which review the subject thoroughly (Howland and Richards, Muskens). Muskens has collected a large number of fatal cases of chloroform poisoning and gives a very elaborate review of the literature. Müller gives a long series of experiments with various anæsthetics, but his conclusions differ widely from those of Lengeman, who shows that prolonged ether anæsthesia causes no damage to the viscera. Other workers have confirmed Lengeman's conclusions. Many of the chemical problems have been studied by Wells, Howland, and others. Experiments by Stiles and M'Donald show that the rabbit is quite susceptible to chloroform poisoning, and the pathology is similar to that described below as found in dogs and man. Ostertag gives experiments on many different animals—rabbits, guinea-pigs, pigeons, rats, cats, and dogs. He found the same lesions in all, but his conclusions were wrong. He considered the fatty degeneration of the heart to be the essential lesion and the liver changes to be secondary.

I. Chloroform Poisoning in Dogs.

In this series of experiments the cases of severe or fatal chloroform poisoning are here brought together for study, and brief reports of the characteristic cases follow.

The method was practically the same in all of these experiments. The animals were all healthy at the beginning of the experiments. No morphia was administered. Anæsthesia was begun with ether because of the ease with which an animal can be killed with chloroform in the early stages of narcosis. Chloroform was given to produce light anæsthesia only, the animals moving the legs or head slightly during the major part of all anæsthesias. Muscular twitchings were found to be evidences of poisoning and high susceptibility as a rule, but not necessarily of deep anæsthesia. Animals were kept under close personal observation during all the experiments. Autopsies were held immediately after death. In case the animal was sacrificed, this was accomplished by ether anæsthesia and bleeding from the jugulars. Tissue was preserved in Zenker's fluid and in formalin, the latter especially for the study of fat. The chloroform used was Mallinckrodt's purified chloroform for anæsthesia "M. C. W."

Delayed Chloroform Poisoning.

Dog 19, small fox terrier, bitch, weight 14 pounds.

March 11. Anæsthesia (ether start). *Chloroform* for 2½ *hours;* 1.25 *ounces* used. Anæsthetic well taken and recovery was rapid.

March 12. Seems rather sick, a little vomiting.

March 13-14. Improving slowly, no vomiting.

March 15. Anæsthesia (ether start). *Chloroform* for 1½ *hours;* 1 *ounce* used; anæsthetic well taken, recovery rapid, lively and active in afternoon.

March 16. Much vomiting and some diarrhœa.

March 17. Drowsy and dull all forenoon; died 5.30 p. m.

Autopsy.—Dog is very well nourished. Serous cavities are quite normal. Thorax, heart and lungs normal. Spleen, pancreas, and kidneys normal. Stomach shows a deep red, swollen mucosa, but no hemorrhages. Duodenum: here are a few superficial erosions, measuring 5 x 2 mm., just below the pylorus. They involve the mucosa only, and there has been but little hemorrhage. Microscopical section shows a little superficial necrosis of the mucosa. Intestines are normal.

Liver is enlarged, pale and very fatty looking. On section the lobules are very sharply outlined with a deep red, clean-cut center and an opaque, yellowish, swollen margin. Gall bladder and bile ducts are normal. Microscopically there is extensive central necrosis, about three-fifths of all the liver cells being killed and appearing as pink-staining hyaline masses. Wandering cells of all types have invaded these areas about the hepatic or efferent veins. There are great numbers of polyblasts and many giant cells surrounding or invading the areas of necrosis. The peripheral liver cells (those about the portal structures) are greatly damaged and full of fat vacuoles. There are numerous mitotic figures indicating a vain attempt at repair of this extensive injury. The bile ducts are unchanged. The areas of central necrosis contain no fat (fat stain, Sudan III) or at most only a few very fine droplets, but the liver cells in the periphery of the lobule are full of large and small fat droplets. This organ contains practically not a single normal liver cell, and may well be called a condition of *acute yellow atrophy.*

ACUTE CHLOROFORM POISONING.

Dog 32, mongrel, Scotch terrier, male, weight about 22 pounds.

May 5. Anæsthesia (ether start). *Chloroform* for 2 *hours;* 1 *ounce* used. Anæsthetic not very well taken.

May 6. *Chloroform* anæsthesia 1 *hour and* 15 *minutes. Half an ounce* used. In the afternoon the dog is vomiting and looks quite sick.

May 7. The dog is vomiting frequently, appears weak and drowsy. Staggers when walking. Died at 11 a. m.

Autopsy at once. Animal is very well nourished. The peritoneal cavity contains 30 to 40 cc. of fresh, unclotted blood. The omentum contains numerous small ecchymoses, which are found as well below the serosa of the stomach and in the neighborhood of the pancreas. Some of these small hematomata measure 1 to 1.5 cm. in diameter. Thorax and lungs are quite normal in gross. *Heart* is pale and rather flabby; otherwise normal. Microscopically the muscle fibres show much fragmentation. Fat stain reveals great numbers of fine droplets between the muscle fibres everywhere. *Spleen* is normal in gross. Microscopically the spleen pulp contains a great many polymorphonuclear leucocytes and much yellow, granular, refractile pigment. *Stomach* contains mucus mixed with black, tarry material which adheres to the mucosa. There are no ulcers in the mucosa, but a few superficial erosions. Duodenum and intestines are normal. *Kidneys* appear normal in gross, but the medullary rays of the cortex are rather opaque and yellowish. Microscopically the section is normal. Fat stain shows the convoluted tubules (distal to the glomeruli) to contain fine droplets of fat in small amounts. The straight tubules in the medullary rays contain large amounts of fat. *Bone marrow* of femur is deep red and uniform. Microscopically there are enormous numbers of polymorphonuclear leucocytes, whereas the red cell elements are inconspicuous. *Pancreas* is of normal size, but the parenchyma is of a delicate grayish pink. Scattered through the parenchyma are little chalky opacities of minute size. They are found only in the pancreas or in the fat close to the pancreas. They are not present in the omentum or peritoneal fat elsewhere. They are evidently small fat necroses, and are especially numerous close to the duodenum. Microscopically the pancreatic acini at the margin of many of the lobules show hyaline necrosis with invasion of this tissue by polymorphonuclear leucocytes. The fat adjacent to such areas shows the usual picture of fat necrosis outlined by a border of fragmenting and wandering cells. The centers of the pancreatic lobules seem to escape this necrosis. The retroperitoneal glands draining the region of the pancreas show areas of hemorrhage and opacities due to necrosis. *Adrenals* are normal in gross. Microscopically there are many polymorphonuclear leucocytes in the fascicular zone of the cortex. The medulla is normal.

Liver.—The capsule is thin. On the upper surface of the liver is a recent subcapsular hemorrhage of lenticular shape, measuring about 3 cm. in transverse diameter. There is a larger hematoma on the lower surface of the liver lobe close to the gall bladder, measuring 8 x 6 x 1.5 cm. This has ruptured into the peritoneal cavity, and from this evidently came the blood found in the peritoneal cavity. The cut section shows a very conspicuous lobulation. The lobules are enlarged, uniform in appearance, and very sharply marked out, presenting a deep red, clean-cut center occupying the greater part of each lobule, and a thin, opaque, yellow peripheral zone in close relation to the portal spaces which are inconspicuous. Microscopically the central necrosis is extreme, involving practically all of the liver cells except a row or two just about the portal structures. Many liver cells in this zone show a little necrotic mass of protoplasm contained within the cell membrane staining sharply with eosin, while the nucleus and remaining protoplasm stains normally. This appears to be partial hyaline necrosis of the liver cell. Stain for fat shows the central necrotic area to contain practically no fat droplets, which, however, are numerous in the marginal zone.

This case resembles closely that described above (dog 19), but is more acute, and the element of hemorrhage is more conspicuous in this case.

CHLOROFORM POISONING.

Dog 10, fox terrier, male, weight 21 pounds.

March 1. Anæsthesia (ether start); *chloroform* 2 *hours;* 2 *ounces* given.

March 2. *Chloroform* anæsthesia ½ *hours;* 2 *ounces* used.

March 3. *Chloroform* anæsthesia 2 *hours;* 2 *ounces* used.

March 4. Very little vomiting and seems well in forenoon. Considerable vomiting and restlessness at noon. In the afternoon *chloroform* anæsthesia 1 *hour;* 1 *ounce* given.

March 5. Dog is very sick. Muscular twitchings are conspicuous. Died at 1 p. m.

Autopsy.—Animal is well nourished. The serous cavities are normal. *Heart* is normal. Microscopically the muscle cells are normal, and there is but very little fatty change. Lungs are normal. *Spleen* is slightly enlarged and presents a mottled, purplish red appearance. Microscopically there are scattered areas of necrosis in the pulp, indicated principally by accumulations of polymorphonuclear leucocytes. Pancreas is normal in gross and in sections. *Kidneys* are normal and contain no fat. *Stomach* is full of dark, bloody fluid. The mucosa is pink, and dotted over with little ulcerations measuring from 2 to 10 mm. in diameter. They present clean-cut edges, and are of oval or round shape. Also there are many small submucous hematomata, which are evidently the early stages of the ulcerations. *Small intestine:* The mucosa is deep red and a little swollen, but there are no ulcers.

Liver is large, swollen, and rather pale. The lobulation is very distinct, each lobule having a red central dot and an opaque, yellow, swollen margin. Microscopically the picture here is somewhat complicated owing to the repeated anæsthesias and consequent repeated necrosis combined with attempts at repair. There are no normal liver cells to be found, even those at the very margin of the lobule show fatty degeneration. The greater part of these liver cells have undergone necrosis. The central portion of the areas of necrosis has undergone solution or has been removed by the numerous phagocytes which are present, allowing great dilatation of the capillaries. The fatty degeneration becomes more striking as we go from the portal areas towards the areas of central necrosis.

NOTE.—This animal was much more resistant to chloroform poisoning than the two preceding animals (dogs 19, 32).

OBSTRUCTIVE JAUNDICE—CHLOROFORM POISONING.

Dog. 8, mongrel dachshund, male, weight about 22 pounds.

January 21. Operation and double ligation of common bile duct close to its entrance into the duodenum.

January 28. Urine is of very high color and contains bile. Feces are clay colored. Sclerotics and subcutaneous tissues are definitely jaundiced.

February 4. *Chloroform* anæsthesia for 2 *hours;* 2.5 *ounces* given. Rapid recovery. The animal seems well.

February 12. *Chloroform* anæsthesia 2½ *hours;* 3 *ounces* given.

February 13. *Chloroform* anæsthesia 2 *hours and* 10 *minutes;* 2.5 *ounces* given. During this anæsthesia an abdominal operation was performed, and a small piece of liver removed for examination. All the serous tissues were deeply jaundiced. The gall bladder was found dilated and very tense. Animal did not make a good recovery and died 36 hours later.

Autopsy February 15. The subcutaneous tissues are deeply jaundiced, but fat is well preserved. The serous surfaces are all

smooth, except for old adhesions about the liver. *Heart* shows many epicardial ecchymoses and is rather pale. *Lungs* and *spleen* are negative. Pancreas shows nothing of importance. *Kidneys* are rather pale.

Liver is much enlarged. The lobules are sharply marked out with a very deep red center, and a yellowish green margin. The common duct is found to be completely obstructed. The gall bladder is dilated and thickened and included in adhesions which undoubtedly prevented its rupture. Rupture of the gall bladder after this operation occurred in several animals. Microscopically the piece removed 36 hours before death shows extensive degeneration and necrosis of the central three-fourths of the liver lobule. There is extensive fatty degeneration in the liver cells at the periphery of the lobule. No mitoses are seen. The bile canaliculi are conspicuous, dilated with brown colloid material. Wandering cells are numerous in the areas of necrosis. Tissue removed at *autopsy* shows many mitoses in the peripheral zone of well-preserved liver cells; otherwise the appearance is practically the same as above.

NOTE.—Obstruction to the common bile duct seemed to influence in no way the lesion produced by chloroform. What part the operation played in causing the animal's death is uncertain, but probably inconsiderable.

CHLOROFORM POISONING WITH HEMORRHAGES.

Dog 18, small mongrel, male, weight about 15 pounds.

March 8. *Chloroform* anæsthesia 2 *hours*, 1.5 *ounces* given. Anæsthetic well taken. Considerable vomiting in the afternoon.

March 9. *Chloroform* anæsthesia 1 *hour and* 20 *minutes*, 0.5 *ounce* given. Animal died very suddenly during anæsthesia, although no chloroform had been given for 10 minutes before death.

Autopsy.—Thorax and abdominal cavity are normal. Heart, lungs, and spleen in gross and in sections are normal. *Pancreas* appears somewhat congested and shows a few minute yellow opacities showing through the peritoneum, probably fat necroses. The sections show nothing abnormal. The kidneys are normal. Stomach, mucosa is pale and covered with bile-stained material. The *duodenum* shows a deep red, swollen mucosa extending from the pylorus to the bile papilla, and in this area are two superficial ulcerations in the mucosa measuring 5 x 2 mms. The jejunum shows considerable swelling and congestion, but no ecchymoses nor ulcers.

Liver is greatly swollen and deep red in color. There are two subcapsular hemorrhages of lenticular shape, the larger measuring 20 x 15 x 3 mm. The cut section shows a very sharp lobulation, each lobule showing a deep red dilated central portion and a thin yellow peripheral zone. The organ is quite friable. Microscopically the lobules show a hyaline necrosis involving about one-half of the liver cells. The capillaries are conspicuous in the areas of central necrosis, and there are a few polymorphonuclear leucocytes and mononuclear wandering cells. Fat stain shows a good many droplets in the border zone between the necrotic central areas and the well-preserved peripheries of the lobules.

NOTE.—It is possible that this animal could have recovered from the liver necrosis, but there was a strong hemorrhagic tendency which is usually associated with the very susceptible cases which show acute chloroform poisoning. (See dog 32.)

PREGNANCY, ACUTE CHLOROFORM POISONING AND HEMORRHAGE.

Dog 31, large bull terrier, weight 38 pounds.

May 2. Anæsthesia (ether start). *Chloroform* 2 *hours*. 1.25 *ounces* given. Anæsthetic was poorly taken and there was considerable muscular twitching, although the animal was kept very lightly under so that she moved her head and legs during the entire time.

May 3. Animal seems well. Fetal movements can be felt through the abdomen. In the afternoon slight bleeding from the vagina noticed.

May 4. There had been some bleeding from the vagina during the night, but the animal seemed bright. There was some vomiting and little desire for food. *Chloroform* anæsthesia 1½ *hours*, 11 a. m. to 12.30 p. m.; 0.75 *ounce* given. Death at 2.30 p. m.

Autopsy at once. Animal is very well nourished. The subcutaneous tissues are very pale. The serous surfaces are smooth. *Heart* is dilated. The muscle is pale. Microscopically the muscle cells show a marked fragmentation. Fat stain shows great numbers of fine fat droplets in all the muscle cells. *Lungs*: all the lobes show small purple areas of hemorrhage 2 to 3 mm. in diameter. Microscopically a few of the alveoli here and there contain red blood cells and a few polymorphonuclear leucocytes. *Spleen* is of normal size and general appearance. Microscopically there are a few small focal necroses affecting the centers of the Malpighian bodies and areas in the pulp. These areas show little hyaline, pink-staining foci surrounded by numbers of polymorphonuclear leucocytes. The large megalokaryocytes are numerous in the pulp. *Kidneys* are normal. The medullary rays in the cortex are quite conspicuous as opaque yellow streaks. Microscopically a few of the tubules contain hyaline casts, but there is no scar tissue nor any acute inflammation in the kidney cortex. Some of the convoluted tubules (distal) contain a few small fat droplets, but the straight tubules in the medullary rays contain great amounts of fat. *Stomach*: the mucosa is pale, but shows a few ecchymoses and contains a little "coffee ground" material. The duodenum and intestines are normal.

Liver is large, swollen and friable. It presents the usual mottled appearance due to the conspicuous lobulation, each lobule showing a large red center and yellow, clean-cut edges. Microscopically the condition is practically that of *acute yellow atrophy* (Fig. 1). There are only one to three rows of intact liver cells about the portal structures, and fat stains show these cells to be full of large and small fat droplets. Even these marginal cells are beginning to degenerate, and a few mitoses can be found. The central portions of all the lobules show uniform very extensive hyaline necrosis. There are a good many wandering cells in these areas of necrosis. These cells are especially numerous in the immediate neighborhood of the blood vessels, from which they are evidently emigrating. There is little fat in the areas of necrosis.

Uterus fills up the greater portion of the abdominal cavity. The serous surface is smooth. The walls are thin and translucent, through which can be seen large blood clots. Incision shows the lumen to be full of clotted and fluid dark purple blood and eight pups. The placenta in each case has begun to separate from the uterine wall, and there has been more or less hemorrhage from this circular zone of separation. The middle zone of each placenta is attached loosely to the uterine wall, but can be separated easily from it. Microscopically the uterine wall and mucosa are normal. *Placenta*: the maternal edge of this organ shows an extensive fatty deposit in the epithelium covering the villi, but in addition there is a well-marked zone of necrosis in this same area. It is best seen associated with the thin zone of hemorrhage, which shows in the section. The remaining portion of the placenta is quite normal, and there is neither fatty degeneration nor necrosis.

Fetuses are all of the same size and general appearance, evidently about two or three weeks before term. Dissection shows the same condition in all. The serous cavities and viscera are quite normal. Microscopically the lungs and thymus are normal. Kidneys are normal. Some of the larger collecting tubules contain fat droplets. Heart: fat stain shows a deposit of small droplets in the muscle cells, not of an extreme grade, however.

Liver.—There is no evidence of any necrosis. In the connective tissue about the portal vein are accumulated a good many polymorphonuclear leucocytes. Fat stain shows a few small drops

in the neighborhood of the central venules of the lobules. Blood formation is still going on actively, and the liver capillaries contain great numbers of marrow cells and nucleated red cells, the megalokaryocytes being very conspicuous.

NOTE.—This case indicates that chloroform is just as toxic to a pregnant animal as to a normal animal. There is a zone of necrosis on the maternal side of the placenta which probably effected the placental separation and hemorrhage. The fetuses show no evidences of chloroform poisoning.

Summary.—Chloroform poisoning in dogs resembles that condition in human beings. The animal recovers from the anæsthetic and may appear quite well, then begins to vomit and may vomit blood. Diarrhœa may be present. The animal becomes more and more toxic and dies in one to four days. Post-mortem examination shows a uniform picture.

The *liver* shows the lesion of importance—a central hyaline necrosis, which may be so extreme as to involve all the liver cells except a row or two about the portal spaces. Fatty degeneration may be slight or extreme (Fig. 2) but is most intense in the boundary zone between the central necrosis and the intact liver cells about the portal spaces. There may be ecchymoses in the parenchyma or extensive subcapsular hemorrhage. The bile ducts and gall bladder are normal. *Kidneys* may show a little fatty degeneration of the convoluted tubules (distal) and considerable fat deposits in the straight tubules of the medullary rays. The latter condition is found in normal dogs but usually in less degree. *Heart* usually shows a little fatty degeneration and fragmentation. *Lungs* may show ecchymoses but usually are normal. *Spleen* may show focal necroses (microscopic). *Pancreas* may show fat and focal necroses, but is usually normal. *Stomach* and duodenum often show small submucous hemorrhages and shallow ulcers from which much blood may escape. The ulcers surely develop as a result of the submucous hemorrhages by a digestion of the mucosa overlying the blood clot. Ecchymoses may be found in any part of the body.

In *pregnancy* there is the usual central liver necrosis, and there may be considerable necrosis and fatty change in the maternal edge of the placenta. This may bring about placental separation and hemorrhage. The fetuses may show no lesions of importance.

II. CENTRAL LIVER NECROSIS.

By this term is meant a necrosis involving the liver cells about the efferent or hepatic venules of the lobules. This series of experiments shows that chloroform is a drug which, administered to dogs by inhalation for a period of one to two hours, will invariably cause central liver necrosis. Opie's experiments and observations on liver necrosis and injections led him to the conclusion that the vascular supply of the liver lobule might be a determining factor in the location of the necrotic zone. Therefore it seemed worth while to study this chloroform necrosis to see how it might be modified by various changes in the blood supply of the liver lobule. With this end in view various dogs were operated upon and the arterial blood supply partially or completely excluded from the liver. Chloroform anæsthesia gave the usual central necrosis. Two dogs with Eck fistulæ, in which the autopsies proved that the portal blood had been excluded from the liver, presented the usual central liver necrosis after chloroform inhalation.

LIGATION OF HEPATIC ARTERY.

Dog 37, small fox terrier pup, female, weight 11 pounds.

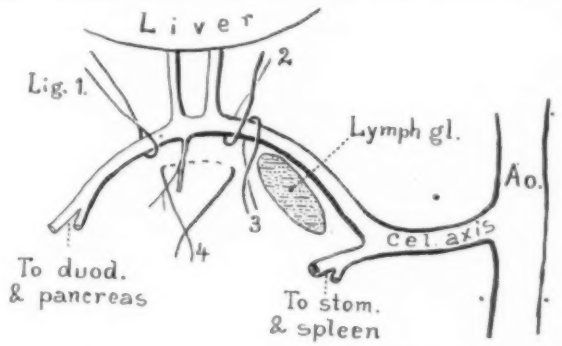
May 26. Operation (ether) and ligation of hepatic artery.

The operation as indicated in the figure was found to be the only satisfactory method of excluding arterial blood from the liver. It was found to be impossible to ligate the hepatic arteries proper, because they are embedded in dense fascia and very intimately associated with the portal system. Ligatures placed as indicated are effectual. It is essential to place ligature 4 as indicated, to include one or more small arterioles given off from the concavity of the arch and supplying the fascia and pancreatic tissue in that neighborhood. The operation is easily performed through a long right rectus incision.

May 28. The dog was well, appetite good. The wound is healing.

June 9. *Chloroform* anæsthesia 2 *hours;* 0.5 *ounce;* well taken.

June 10. Operation (ether), abdominal incision and removal of a large, wedge-shaped piece of liver. Microscopically (Fig. 4) the liver lobules show the usual picture of central necrosis involving



one-half of each lobule. The liver cells are pink-staining and hyaline, their nuclei showing pyknosis or fragmentation. There are many polymorphonuclear leucocytes in the areas of necrosis. Fat stain shows a conspicuous middle zone of fatty degeneration in which the liver cells contain large and small fat globules. The liver cells about the portal spaces are quite normal.

June 12. Recovery was rather slow, but steady. Abdominal wound broke down with exposure of the muscle.

June 21. Dog quite well and fat. Wounds are completely healed. Killed (ether and bleeding from jugulars). Pieces of liver removed at once and placed in fixing fluids. Then preparations were made at once for *arterial injection* with a vermilion gelatin injection mass. This injection mass is forced into the blood vessels under a pressure of 100 to 120 mm. of mercury. It is quite fluid when warm and easily passes the capillary bed. It solidifies when the animal is placed on ice, thus marking out the blood vessels with bright red cylinders of gelatin. The injection cannula is tied into the aorta just above the diaphragm. The aorta is clamped just above the renals. A clamp is placed on the vena cava below its entrance into the liver and on the portal vein just below the splenic branch. When pressure is applied the injection mass flows rapidly into the vessels of the stomach, pancreas, spleen, and intestine, but none escapes from the cut section of the liver. After some time a little of the injection mass mixed with blood escapes from the cut section of the liver. It is found that this comes from the portal veins by passing through the splenic capillaries, splenic vein, and portal branches of the liver. After hardening in the ice box, careful dissection showed that the

hepatic arteries contain no injection matter, and are completely cut off from the arterial tree. (See text figure.)

Liver. There are a few old adhesions around the sites of the two operations. Elsewhere the serous surface is smooth. The organ has a normal appearance. The lobulation is clean cut. The centers of the lobules are perhaps a little conspicuous, but the greater part of the parenchyma is brown and translucent. Microscopically (compare dog 40) the *repair* is almost complete (11 days' interval). The lobules are about normal size, but the centers are not quite filled in (Fig. 5). Here is seen a loose reticulum including a little yellow, granular pigment, and a few mononuclear wandering cells (polyblasts). Fat stain shows in the center only a few droplets of fat. Scattered here and there through the lobules in the middle or central zones are little nests of mononuclear cells (Fig. 5). Careful examination shows usually a central hyaline mass staining a diffuse pink about which the mononuclears have gathered. Some of these masses show deposits of lime salts. They are usually the size of two or three normal liver cells, and are undoubtedly remains of dead liver cells which have not as yet been removed but are surrounded by phagocytes. No mitoses are seen in the liver cells. The bile ducts everywhere are quite normal.

NOTE.—It is not easy to exclude the arterial blood from the liver, and this can only be assured by some control as the above injection, which shows that this operation did completely shut off the hepatic artery. The necrosis is of the usual type, as is also the process of repair, which will be discussed at some length in the following section, and reference will be made to this experiment.

LIGATION OF THE HEPATIC ARTERY.

Dog 34, mongrel, male, weight 20 pounds.

May 11. Operation exactly as described for dog 37.

May 13. Dog eating well. Wound healing.

May 14. *Chloroform* anæsthesia 2 *hours;* 1 *ounce* given. Anæsthetic well taken.

May 15. Animal killed (ether and bleeding from jugulars). Pieces of liver removed at once and injection through aorta as described in dog 37. Careful dissection showed that the hepatic arteries were completely excluded from the arterial stream.

Liver presents the usual appearance seen in chloroform poisoning. It is swollen and friable. The lobulation is very distinct. Microscopically the liver lobules show a central hyaline necrosis involving three-fourths of the liver cells. Many polymorphonuclear leucocytes have invaded the areas of necrosis. Fat stain shows fine droplets in the protoplasm of the damaged cells.

LIGATION OF HEPATIC ARTERY.

Dog 38, fat fox terrier, male, weight 18½ pounds.

May 28. Operation (ether): ligation of hepatic artery exactly as indicated for dog 37. These two operations were done on the same day and under exactly similar conditions.

May 30. Dog is well; wound is slightly infected but healing.

June 8. Dog is well; wound is healed.

June 10. Operation (ether): abdominal incision and removal of a large wedge-shaped piece of liver tissue.

Liver is of normal appearance in every respect. Microscopically (Fig. 3) perhaps there is a very little atrophy of the liver cells in the center of the lobules where there are a few small droplets of fat. This indicates that ligation of the hepatic artery causes no appreciable effect on the liver.

LIGATION OF HEPATIC ARTERY (PARTIAL)—CHLOROFORM POISONING.

Dog 30, mongrel, male pup, weight 20 pounds.

April 22. Operation and ligation of hepatic artery as usual (see text figure). There was considerable bleeding and handling of the viscera.

April 23. Dog appears well. No vomiting.

April 29. *Chloroform* anæsthesia 2 *hours;* 1 *ounce* given; anæsthetic well taken.

April 30. Good recovery, no vomiting. Dog is active.

May 1. *Chloroform* anæsthesia 2 *hours;* 1 *ounce* given. Animal was alive at midnight.

May 2. Found dead in room, but body still warm.

Autopsy.—Peritoneal cavity is full of bloody fluid (75 cc.). There are no clots. The omentum contains numerous small hemorrhages and ecchymoses. Heart is normal. *Lungs*: there are a few small hemorrhagic patches in the right base not over 1 cm. in diameter. Microscopical sections show some œdema and congestion, and a slight exudate of polymorphonuclear leucocytes in a few of the alveoli. *Thymus* is large, œdematous, and contains numerous indefinite hemorrhages. Spleen, pancreas, kidneys show no change of importance. *Stomach* contains a large amount of fluid and "coffee ground" material. The mucosa shows a few superficial erosions and submucous ecchymoses. The duodenum above the bile papilla shows ecchymoses and considerable congestion. Microscopically there are many clumps of polymorphonuclear leucocytes all through the mucosa, and evidence of focal necrosis.

Liver.—Careful dissection of the structures at the hilum shows that the operation did not completely exclude arterial blood. Ligature 4 was not efficient and did not occlude a small arteriole communicating with the pancreas. Probably a small amount of arterial blood gained entrance into the liver by this means, but surely the greater part of the arterial blood was cut off. The liver in gross presents the usual appearance seen in extreme chloroform poisoning. It is large, mottled and very friable. The lobules are very conspicuous. There are a few old adhesions about the site of operation. Microscopically the liver lobules show a complete hyaline necrosis involving more than two-thirds of the liver cells. The marginal liver cells are well preserved, and the line of demarcation between the areas of necrosis and well-preserved liver cells is very sharp. There are many mitoses.

NOTE.—It is unlikely that the small patches of bronchopneumonia had any effect upon the liver. This is a typical case of acute chloroform poisoning (compare dog 32) in which hemorrhage is a striking feature.

LIGATION OF HEPATIC ARTERY (PARTIAL).

Dog 26, small mongrel, male pup, weight 12 pounds.

April 6. Operation (ether): ligation of hepatic artery. Ligatures 1 and 2 only were applied (see text figure).

April 10. Dog is well. Wound is clean.

April 23. Dog is fat and healthy. *Chloroform* anæsthesia 1½ *hours;* 0.5 *ounce* given. Anæsthetic taken poorly. Heart was quite irregular.

April 24. Dog seemed well and lively; no vomiting.

April 26. *Chloroform* anæsthesia 1½ *hours;* 0.5 *ounce.*

April 27. Dog appears bright and active. Killed (ether and bleeding from jugular). Pieces of liver saved in fixing fluids, and the aorta injected at once with the vermilion injection mass (see dog 37). After cooling on ice, dissection shows that there are two small arterioles opening from the concavity of the arch (see text figure), through which the injection mass entered the hepatic arteries. They were very small and could have supplied but little arterial blood to the liver. The viscera are quite normal except the liver.

Liver presents the usual appearance. It is very opaque, swollen, and yellow. The lobulation is conspicuous. Microscopically fat stain shows an unusual amount of large and small fat droplets throughout the central portions of the lobules, affecting at least three-fourths of the liver cells. The usual hyaline necrosis is found in the central half of the lobules. The liver cells about the portal spaces are normal in appearance. Other experiments in which the same results were obtained will not be added.

Summary.—It has been shown by Janson that ligature of the hepatic artery causes no appreciable change in the liver of the dog. Our experience confirms his findings. The lack of arterial blood has no influence upon the type of central necrosis produced by chloroform inhalation, nor has it any influence upon the regeneration of the liver following this injury.

ECK FISTULÆ.

Through the kindness of Dr. Carl Voegtlin we were able to perform autopsies on two dogs with Eck fistulæ, the animals having been under observation for 10 to 11 weeks. Autopsies showed all the viscera to be normal in gross except the liver. Microscopical sections show nothing of interest except in the liver. The heart, lungs, spleen, pancreas, intestines, and kidneys were quite normal.

In one of the dogs the fistula between the portal vein and vena cava was quite small (4 x 6 mm.), and the ligature about the portal vein above the fistula was not effective, the opening admitting only the points of the scissors. In the other animal the fistula was quite large and the ligature of the portal vein was efficient.

The *livers* were practically the same in both cases. The organ is small, flabby, and rather tough. The lobules are small, presenting a brown, translucent edge and minute central yellow dot. Microscopically there is considerable atrophy and fatty degeneration of the central half of the liver lobule (Fig. 6). The animals used in the following chloroform experiments were operated upon by Dr. John Homans. We wish to thank him for his kindness in performing this difficult operation for us.

Dog 27, large brindle bull-dog, male, weight 32 pounds.

April 20. Operation (ether): Eck fistula established (Dr. Homans).

Dog made a good recovery. There was no vomiting. Wound slightly swollen.

April 23. Dog is well. In the afternoon *chloroform* anæsthesia 1 *hour;* 1 *ounce* given. Anæsthetic well taken and recovery rapid.

April 24-25. Dog active and well.

April 26. *Chloroform* anæsthesia 1½ *hours;* 1.2 *ounces* given. Anæsthetic taken well.

April 27. Animal appears normal.

April 29. Operation (ether): abdominal incision and removal of a wedge-shaped piece of liver.

Liver.—The gross appearance is not very abnormal. Microscopically fat stain shows many large fat droplets throughout the central three-fifths of the liver lobules. The marginal zone is free from fat and normal in all respects. Many of the central cells are shrunken, and some show complete hyaline necrosis. These necrotic cells are surrounded by phagocytes. There are many mitoses in the peripheral liver cells.

April 30. Dog is rather sick. Appetite is poor.

May 1-7. Slow improvement. There is some diarrhœa.

March 10-14. Considerable vomiting; gradual loss in weight; animal looks sick.

May 17. Animal losing weight and getting weaker. *Chloroform* anæsthesia 1½ *hours;* 1 *ounce* given. Anæsthetic well taken.

May 18. Animal killed (ether and bleeding from jugular).

Autopsy.—There are old adhesions about the site of the operation. Careful dissection of the portal structures shows that the fistula is efficient, and the ligature on the portal vein above the fistula completely closes the vein. The portal branches in the liver are greatly shrunken but contain fluid blood. The vena cava above the site of operation is somewhat thickened. *Heart* is quite normal. Sections show no fat. *Lungs*: both posterior lobes show large, deep red patches of bronchopneumonia, some of them measuring 4 x 2 x 1 cm. Microscopical sections show a bronchopneumonia in which there is a very little fibrin, but considerable œdema and many polymorphonuclear leucocytes and red blood cells. *Spleen* is perhaps a little increased in size. Microscopical sections show a good many polymorphonuclear leucocytes all through the pulp. The solitary follicles are normal. *Pancreas* is quite normal. *Kidneys* appear normal. The medullary rays are rather opaque. Sections show a good deal of fat in the straight tubules of the medullary rays. Stomach is normal.

Liver is small and quite pale. It is flabby and rather tough. Microscopically (Fig. 7) the central three-fifths of the lobules shows fatty degeneration and necrosis. The margin of the lobules shows normal liver cells. There are a good many phagocytes in the central area of necrosis, some of them containing granular, yellow pigment. The bile ducts are all normal.

NOTE.—In the sections at autopsy there is almost no evidence of the damage done to the liver by the chloroform administration (April 23), and evidently the repair was complete. Perhaps the large phagocytes containing yellow, granular pigment are the only remnants of this change (compare dogs 37 and 40 for details of this repair).

Dog 35, large, strong, brindle bull-dog, male, weight 35 pounds.

May 20. Operation (ether): Eck fistula established (Dr. Homans).

May 21-30. Dog doing well. Wound healing. No vomiting.

June 1. Operation (ether): abdominal incision and removal of a large wedge-shaped piece of liver for microscopical study. Wound partly closed, then *chloroform* anæsthesia started. Chloroform anæsthesia for 3 *hours;* 0.7 *ounce* only was given. Anæsthetic well taken. At the end of the chloroform administration a second piece of liver was removed for study. Abdominal wound closed.

Liver in gross appears small, deep red in color, and rather tough. Microscopical sections removed before and after administration of chloroform are exactly similar (Fig. 6). The liver lobules show considerable central atrophy of a very uniform type. There are a few small fat droplets in these central areas. There is no necrosis.

June 2. Dog rather weak but seems quite well otherwise. No vomiting. Killed in the afternoon (ether; bleeding from jugulars).

Autopsy.—The serous cavities are normal except for adhesions around the sites of the operation. Thorax, heart, lungs, pancreas, stomach, intestine are quite normal. Spleen is of normal size. Microscopically there is a good deal of yellow, granular pigment throughout the pulp. The *kidneys* are normal in gross. Section shows a little fat in the straight tubules of the medullary rays, and a few fine fat droplets in the convoluted tubules (distal).

Liver is small, rather pale, and tough. The lobules are quite small and show minute yellow central specks. Microscopically there are very small but quite definite hyaline central necroses of the usual type. Some of the lobules seem to escape. There are numerous wandering cells in the neighborhood of the necrotic cells. The liver cells in the centers show considerable fatty deposit. The peripheral half of the liver lobules is nearly normal. Possibly the small amount of chloroform given determines the small amount of necrosis found in this case. *Eck fistula*: the opening between the portal vein and the vena cava is quite large, measuring about 12 mm. in long diameter. The edges of this opening are rounded and smooth. Ligature on the portal vein above the anastomosis completely occludes the lumen. The portal branches in the liver are shrunken and contain fluid, deep red blood.

NOTE.—The findings in this experiment are similar to those observed in dog 27. The necrosis, though quite slight in amount, has the usual distribution. The specimen of liver removed before the administration of chloroform acts as an excellent control (Fig. 6) and shows that the establishment of an Eck fistula causes considerable central atrophy and fatty degeneration.

Summary.—Dogs with Eck fistulæ show no lesions of interest except in the liver. All the other organs are normal in gross and microscopically. The *liver* is diminished in size, of normal color, but rather tough. The stroma, bile ducts, and gall bladder are normal. In sections the liver lobules are seen to be decidedly smaller than normal (Fig. 6), and this change is due chiefly to a central atrophy and a little fatty degeneration. *Chloroform* anæsthesia gives a central necrosis of the usual type (Fig. 7), although the poison must have been carried to the liver by the arterial stream alone.

Chloroform Injected into Portal Vein.

Dog 23, small adult, male, weight about 18 pounds.

March 31. Operation (ether): abdominal incision, isolation of a small branch of the portal vein, and injection of 1 *cc.* of *chloroform* into this vein. Abdominal incision closed. The animal was quite drowsy for the next hour. There was considerable vomiting. In the afternoon the animal seems very ill and there are muscular twitchings and vomiting of bile-stained material.

April 1. Dog much improved; appetite is good. No vomiting.

April 2. Dog looks pretty sick. Killed at 5 p. m. (ether).

Autopsy.—All the serous surfaces are normal. Thorax, heart, lungs, spleen, pancreas, stomach, duodenum, and kidneys are quite normal in gross and in sections.

Liver.—The organ is pale and mottled with scattered areas of opacity, which are swollen, some of the larger ones measuring over 1 cm. in diameter. The tissue is quite opaque and outlined with a thin rim of hemorrhage. Where these areas touch on the capsule of the liver there are fibrinous adhesions overlying the surface. Elsewhere the liver lobules seem of normal size and show small central yellow dots. Microscopically (Fig. 11) there are extensive hyaline necroses scattered through most of the sections. Some of these are quite large, involving many lobules completely. Other lobules show only a thin rim of hyaline necrosis involving the tissue adjacent to the portal vein. In other areas are seen little round focal necroses involving only a few liver cells, but usually situated close to a portal vein and definitely in the periphery of the lobules. These areas of necrosis present the usual appearance and are full of various wandering cells. The centers of all the liver lobules show a little fatty degeneration, but fat is not present in the areas of necrosis.

Chloroform Injected into Hepatic Artery.

Dog 36, fox terrier, male, weight 15 pounds.

May 21. Operation (ether): abdominal incision. *Chloroform*, 1 *cc.*, injected into the hepatic artery about the location of ligatures 2 and 3 (compare text figure, dog 37). Some of this chloroform undoubtedly was carried to the duodenum and pancreas, but most of it into the liver. The wound was closed and animal recovered pretty rapidly.

May 22. Dog is drowsy and sick.

May 23. Dog is improving slowly, but seems rather dull. Dog killed at noon (ether).

Autopsy.—The serous cavities are all normal. There is some hemorrhage and œdema in the region of injection at the hilum of the liver. Heart, lungs, spleen, and kidneys are quite normal. *Stomach* and *duodenum* show numerous flame-shaped hemorrhages just below the serosa. The mucosa is swollen, deep red, and there is a thin rim of hemorrhage apparently in the submucosa. This process extends some distance down into the small intestine. There is no ulceration of the mucosa. Microscopically the rim of hemorrhage and necrosis is found to be not in the submucosa, but just at the base of the gland tubules of the mucosa. *Pancreas* is swollen and of a pinkish color. It is speckled with little fat necroses and small ecchymoses. Microscopically there are numerous focal, hyaline necroses of considerable size, involving several acini at a time. These areas of necrosis are especially numerous at the edge of the lobules. Polymorphonuclear leucocytes are particularly numerous at the edge of these necroses. Small fat necroses are usually associated with these areas.

Liver is soft and flabby, and a little bit diminished in size. The left lobes are much more involved than the right. The liver tissue here has a mottled appearance. The normal liver tissue contrasts with the areas of opacity, which are usually of small size and sharply marked out. Hemorrhage is not a striking feature. These lines and streaks of opacity appear to follow the larger portal structures, presenting a tree-like appearance in some sections. The right lobes are rather pale but translucent-looking, and the lobules are of normal size. There is evidently very little or no fatty degeneration here. Microscopically in some areas one sees massive necrosis involving several adjacent lobules completely. In some places are seen definite peripheral necroses involving liver cells adjoining portal spaces, but close to these same areas may be seen more numerous clean-cut central necroses involving about one-half of the liver lobule. A study of many sections shows that the areas of central necrosis are more numerous than those of peripheral necrosis. The areas of necrosis present the usual picture. Many of the dead liver cells have been in great part dissolved and replaced by wandering cells. The bile ducts show no abnormality. Fat stain shows no change of importance.

It will be seen that injection of chloroform into the portal vein can give rise to scattered areas of *peripheral* necrosis, while injection into the hepatic artery may cause not only *peripheral* necrosis, but *central* necrosis as well. The picture, however, in no way suggests that found in eclampsia, where we have evenly distributed and uniform *peripheral* necroses corresponding to the uniform *central* necroses produced by chloroform anæsthesia.

Is the Liver Necrosis Produced during or after Chloroform Anæsthesia?

Our experiments on this point are not conclusive.

Dog 39, small fox terrier, female, weight 15 pounds.

June 2. Operation (ether): removal of a wedge-shaped piece of liver. *Chloroform* anæsthesia was then begun and continued for 3 *hours;* 0.8 *ounce* given. At the end of this chloroform anæsthesia a second piece of liver was removed.

Liver appeared absolutely normal at the beginning and end of the chloroform anæsthesia. Microscopically both pieces of liver are normal. The protoplasm and nuclei of the liver cells in all parts of the lobule stain normally and similarly in the two specimens.

June 3. Dog appears well; animal given nothing but water. Operation (ether): the old wound is reopened and a third piece of liver is removed. The peritoneal cavity is normal.

Liver in gross has the usual appearance seen in chloroform necrosis. Microscopically the liver lobules show a central hyaline necrosis involving one-half of the parenchyma. The cell protoplasm as a rule is hyaline and bright pink-staining. Many of the nuclei show fragmentation, but the majority show extreme pyknosis. Some of the cells in the very center of the lobule seem to be pretty normal, and the nuclei are not much changed. Many leucocytes are present in the capillaries, particularly in the middle zone, where the nuclear fragmentation and hyaline change of the protoplasm is most marked.

June 4. Animal is rather sick. Killed at noon (ether), 44 hours after removal of control piece of liver, which was normal.

Autopsy.—All the viscera are normal except the liver. There are fresh adhesions around the abdominal incision.

Liver presents the usual picture. The lobulation is very clean cut. Microscopically the liver lobules show the usual uniform

complete central necrosis involving two-thirds of the lobule. All the liver cells in these areas have undergone complete hyaline necrosis, and there are large numbers of wandering cells in the central areas. There is a well-marked middle zone of fatty degeneration.

NOTE.—Compare with this experiment dog 40 (see below) and dog 35 (Eck fistula), in which similar experiments showed that the liver cells, as far as could be determined by the microscope, were normal at the end of a long chloroform anæsthesia. This finding suggests that the liver necrosis might be due to some metabolic products formed in the organism as a result of the chloroform anæsthesia.

This phenomenon may be explained in many ways, but not quite satisfactorily. Wells has advanced an ingenious and attractive hypothesis for this action of chloroform: That the drug inhibits the synthetic activity of the cell but not the activity of its enzymes, and the cell digests itself. He believes the oxidazes to be particularly involved. If the cell digestion is due to an inhibition of the cell activity effected by the chloroform, this autolysis must be active only during the administration of the drug and during that time must have completely destroyed the cell life. It is possible but perhaps improbable that this autodigestion could destroy the life of the cell without injuring any of its staining properties.

Longcope has made some interesting experiments on autolysis *in vitro* showing that blood serum inhibits autolysis of liver cells, but has reported no observations on the action of chloroform.

A second possible explanation of this delay in appearance of the liver necrosis is the following: The chloroform causes a true cell necrosis *in situ*, as may be illustrated by the action of alcohol or any fixing fluid on the surface of the liver. The inflammatory reaction occurs in a few hours, and the dead cells become hyaline-looking by absorption of the body fluids and a coagulative process.

Experiment (dog 39) shows that 20 hours after anæsthesia the liver cells show definite but not typical signs of hyaline necrosis. The necrotic areas show most extensive nuclear fragmentation and hyaline change in the *peripheral* portion, where the dead liver cells are in contact with the living and are being invaded by the wandering cells. The liver cells in the very centers of the lobules may appear almost normal under the microscope, yet we know they are dead, and during the next 24 hours they assume the usual hyaline, necrotic appearance. But if chloroform is injected directly into the portal vein it causes a necrosis which can be recognized by the microscope at the end of two hours (see following experiment, dog 15).

Dog 15, medium-sized mongrel, male.

March 2. Operation (ether): isolation of a small branch of the portal vein and injection into this vein of 6 cc. of *chloroform*. The animal was profoundly shocked and heart stopped beating. Massage through the diaphragm started the heart beating again. The dog lived for 2 hours after the injection of chloroform.

Autopsy.—The viscera are all negative. *Liver* presents a remarkable mottled appearance, grayish red, swollen areas alternating with darker purple, more normal-looking liver tissue. Microscopically fat stain shows nothing except a few fat droplets in the epithelium of the bile capillaries. There is a widespread destruction of the parenchyma in irregular patches, usually about the portal vessels. Here the liver cells look pink and glassy, and the nuclei are dull and pale-staining. The protoplasm is not hyaline, but takes more of the pink stain than normal. There is but very little cell reaction about these areas of necrosis.

NOTE.—In this experiment the liver cells were killed suddenly by the direct action of the chloroform, and such cells 2 hours after the action of the chemical show disappearance or a very faint staining of the nuclei. Such lesions after a duration of 24 hours (see dog 23) appear very like the hyaline central necroses produced by chloroform anæsthesia. The liver cells in both cases are hyaline, pink-staining, refractile, and surrounded by many wandering cells.

GENERAL DISCUSSION OF LIVER NECROSIS.

The above experiments show conclusively that the vascular supply of the lobule has no relation to the character and distribution of chloroform necrosis—a typical example of central liver necrosis. It is well known that central necrosis is common but mid-zonal and peripheral necroses are rare in human and animal pathology. We have found no record of experimental production of mid-zonal or peripheral necroses. How may we explain the apparent specificity of a poison like chloroform, which invariably exerts its harmful effects first on the very central cells, with a progressive involvement of the neighboring ones? There are many possibilities:

1. That the bile ducts drain off the harmful products and more effectually protect the margins of the lobules.

2. That the drug has a specific action on the central liver cells.

3. That the lack of arterial blood or the accumulation of waste products in the blood renders the cells supplied by this blood more susceptible to the poison.

4. That the activity of the poison determines its point of attack—all poisons are brought to the periphery of the lobule and the more powerful ones (for example, the eclamptic poison) may attack the cells first encountered.

There is no support for the view that the bile ducts drain the portal fraction more effectually and thus prevent peripheral necrosis. Dog 8 (see above), with complete obstruction of the common bile duct, presented the usual chloroform necrosis.

There is no very strong evidence for a true specific action of chloroform, for it will cause necrosis of the liver cells in the middle zone *after* the cells in the center have undergone necrosis. In fact by prolonged chloroform anæsthesia in animals we may kill practically every liver cell except a single row or two about the portal spaces (see dog 31, above, and the human case 2689, Figs. 1 and 12).

There are many points in favor of the view that the accumulation of waste products in the blood, as it flows from the edge to the center of the lobule, renders the central cells more prone to injury. But the finding of a thin peripheral zone of liver necrosis in eclampsia speaks strongly for either a selective action of the poison or a very powerful poison which acts *immediately* when brought in contact with the liver cells. We may imagine that the weaker or diluted poisons can injure only the central liver cells after prolonged action, as in a long chloroform anæsthesia.

It is possible that a *central* necrosis is determined by both these factors—namely a weak or diluted poison and a concentration of waste products in the center of the lobule.

III. Repair after Central Liver Necrosis.

When a liver is examined in which at least one-half of all the liver cells have been destroyed, that is, all the central cells have undergone hyaline necrosis, it seems obvious that the process of repair will lead to more or less scar formation, with consequent distortion of the liver architecture. Yet such is not the case, and the process of repair will bring the organ back to a normal condition after two to three weeks. It will be shown in cases which follow that after chloroform has been administered sufficient to cause necrosis of the central two-fifths or three-fifths of every liver lobule, the process of repair will begin at once, provided the animal recovers. The necrotic debris is removed by wandering cells or cell enzymes; the remaining liver cells multiply rapidly and replace a greater part of the deficit in six days (Fig. 9), effect almost complete repair in eleven days (Fig. 10), and after three weeks the liver seems quite normal, except perhaps for a few small nests of wandering cells about some of the efferent veins. The bile ducts take no part in this process, and it seems very unlikely that any such necrosis could be responsible for cirrhosis of the liver as seen in man. One observation may throw a little light on this matter. An animal (dog 13) had been given chloroform to produce liver necrosis, then operated upon under ether with removal of a wedge of liver for examination. The wound in the liver was closed with two cat-gut sutures, and the animal was allowed to live for several days. Microscopical sections removed at autopsy six days later showed extensive central necrosis in every lobule and the usual process of repair with no participation of the bile ducts, but around the liver sutures was a different picture. These sutures had caused massive necroses in the liver, due in part to pressure, and many liver lobules showed complete necrosis. Many of the *bile ducts* in such areas had not undergone necrosis, but were sending out buds and sprouts into the nearby tissue, giving a picture very suggestive of an early cirrhosis. As shown above it is possible to cause scattered areas of massive necrosis in the liver by injection of chloroform into the portal vein. Animals in which this has been done repeatedly are under observation to determine whether a true cirrhosis can be produced in this manner.

Repair after Chloroform Necrosis—Eleven Days.

Dog 40, mongrel, male pup, weight 21 pounds.

June 7. Operation (ether): abdominal incision and removal of wedge-shaped piece of liver. The anæsthetic was then changed and *chloroform* given for 2 *hours and* 50 *minutes;* 1 *ounce* given. At the end of this anæsthesia a second piece of liver was removed, and the abdominal incision closed as usual.

Liver before and after anæsthesia is quite normal in gross. Microscopically the pieces removed before and after anæsthesia are exactly similar and quite normal. Fat stain showed a few very fine fat droplets in the cell protoplasm, and a good many fat droplets in the epithelium of the bile ducts. This is a condition normally present in healthy animals.

June 8. Animal is well and active. Operation (ether): the old surgical incision was reopened and a third piece of liver removed. Liver in gross presents the usual picture found in chloroform poisoning. It is swollen, friable, and the lobulation very conspicuous. Microscopically each liver lobule shows a central hyaline necrosis involving about three-fifths of the parenchyma (Fig. 8). There has been invasion by numbers of wandering cells. There is a very conspicuous zone of fatty degeneration between the areas of necrosis and the margin of well-preserved liver cells about the portal spaces. There are no mitoses found.

June 10. Animal seems pretty well. The wound is œdematous. Takes food without vomiting.

June 12. Dog is recovering rapidly and eats well.

June 19. Dog is active and perfectly well. Killed (ether).

Autopsy.—Animal is very well nourished. The serous cavities and viscera are all normal in gross. The stomach is full of food. There are old adhesions about the operation scars. Microscopical sections show nothing of interest except in the liver.

Liver appears normal in gross except for scars and adhesions at sites of operation. The lobules are very distinct and of normal size. The center shows a slight congestion, and the periphery has the usual translucent, brownish red appearance. The consistency is normal. The gall bladder and ducts are normal. Microscopically (Fig. 10) the repair is almost complete. Many of the lobules are quite normal. Some of them show some abnormalities in their very centers. Here the liver reticulum is a little conspicuous and has not been filled in by the proliferating liver cells. The chinks in this reticulum are filled by mononuclear wandering cells and little grains of yellow granular pigment. There are no evidences of any new formation of connective tissue in this region. Here and there in some of the lobules are found little nests of mononuclear cells, but these are few in number and of small size, never occupying a space larger than that occupied by four or five normal liver cells. The bile ducts are normal and the architecture is quite uniform.

Note.—Compare these experiments with dog 37, in which the hepatic artery had been cut off from the arterial tree, yet the repair after the same interval was practically the same in the two animals (Fig. 5). It is remarkable that the remaining liver cells (the peripheral one-fourth) which are not damaged by the chloroform are able to multiply rapidly and repair the liver completely in a space of 11 days.

Repair after Chloroform Necrosis—Six Days.

Dog 13, fox terrier, male.

February 16. *Chloroform* anæsthesia 2½ *hours;* 2.5 *ounces* given.

February 17. *Chloroform* anæsthesia 2½ *hours;* 2.5 *ounces* given. There was considerable vomiting during the night.

February 18. Dog is not feeling well, and there is some vomiting. Operation (ether): abdominal incision and removal of a wedge-shaped piece of liver.

Liver presents the usual picture in gross. Microscopical section shows an extensive central necrosis involving about three-fifths of the liver lobule. This necrosis is of the usual hyaline type, with invasion by many wandering cells. There are a few mitoses in the peripheral liver cells about the portal spaces.

February 19-20. Dog is quite sick and drowsy. Considerable vomiting.

February 21-23. Dog improving rapidly.

February 24. Dog seems well. Animal killed (ether).

Autopsy.—The serous surfaces, thorax, heart, lungs, and spleen are all normal. *Kidneys*: cortex is rather opaque and swollen. Pancreas and intestine are normal.

Liver is of rather small size. The color is a pale yellowish brown. The lobulation is quite regular. The centers of the lobules are rather conspicuous and contain blood. Microscopically (Fig. 9) the peripheral zone of normal liver cells has about doubled in thickness, filling up the greater part of the liver lobules, but the central fifth of each lobule shows a delicate reticulum apparently uninjured by the process of necrosis and repair. The necrotic liver cells have undergone almost complete solution

and disappearance. The loose central reticulum contains a good many large mononuclear wandering cells and a few small grains of yellow pigment. A few of the liver cells contain fat droplets, but the great majority of the liver cells appear normal. Only a few mitoses can be found. Bile ducts are quite normal. Sections made through the healing wound in the liver show the interesting picture above described. About the cat-gut sutures there has been a massive necrosis involving many lobules, and the bile ducts in such areas show beginning proliferation and branching, suggesting the picture seen in cirrhosis of the liver.

NOTE.—By comparing this experiment with the preceding one, it is seen that the repair takes place by a multiplication of the liver cells, thus causing an elongation of the cords of liver cells. This brings about a gradual filling in of the centers of the damaged lobules, the liver cells being pushed in from the marginal zone. There is no connective tissue reaction in such areas, although the large mononuclear cells as well as the polymorphonuclear cells are quite numerous. *The bile ducts do not seem to take part in this process, unless the necrosis has affected all the liver cells of the adjacent liver lobules.*

REPAIR AFTER CHLOROFORM NECROSIS—EIGHTEEN DAYS.

Dog 33, small mongrel, male, weight 16 pounds.

May 7. *Chloroform* anæsthesia 1½ *hours;* 0.6 *ounce* given. Anæsthetic well taken.

May 9. *Chloroform* anæsthesia 1 *hour and* 45 *minutes;* 0.7 *ounce* given.

May 10. The dog looks quite sick. Operation (ether): abdominal incision and removal of a wedge-shaped piece of liver.

The *liver* in gross looks large, swollen, and yellowish. The lobules are large, yellow and opaque. Microscopically there is the usual central necrosis involving one-third of the liver lobule. The liver cells are hyaline in appearance, and surrounded by many wandering cells. The middle zone contains a large amount of fat. There are many mitoses in the well-preserved liver cells.

May 11. Dog is recovering slowly; no vomiting.

May 13. Wound is breaking down, but animal is improving rapidly.

May 16. Dog is quite lively. The wound is granulating.

May 28. Dog is quite well and fat. Operation (ether): removal of piece of liver.

Liver appears quite normal in gross. Microscopically the liver is practically normal and the repair complete. Some of the lobules show a few mononuclear cells in the very centers. Some phagocytes contain a few grains of yellow pigment, and there may be a few polymorphonuclear leucocytes in these areas. The architecture of the liver is quite uniform and regular. The liver cells are normal. Bile ducts are normal.

REPAIR OF LIVER FOLLOWED BY SECOND CHLOROFORM NECROSIS.

Dog 28, mongrel, female, weight 18 pounds. The dog is very strong and active.

April 21. *Chloroform* anæsthesia 1 *hour and* 45 *minutes;* 1 *ounce* given.

April 22. Dog is quite well, no vomiting; *chloroform* anæsthesia 2 *hours;* 2 *ounces* given. Anæsthetic well taken.

April 23. No vomiting, but animal is not very active. *Chloroform* anæsthesia 1 *hour and* 20 *minutes;* 1.5 *ounces* given.

April 24. Operation (ether): abdominal incision and removal of a wedge-shaped piece of liver.

The *liver* in gross presents the usual picture of chloroform necrosis. Microscopically the liver lobules show extensive necrosis and solution of the liver cells involving about one-half of each lobule. There are many hyaline necrotic liver cells surrounded by mononuclear and polymorphonuclear wandering cells, but the greater part of the dead liver cells has been removed, leaving a rather conspicuous reticulum and capillary network which contain many wandering cells. The peripheral cells of the lobules show extreme fatty change. Mitoses are not very numerous.

April 25-26. Dog recovered very rapidly and seems quite normal.

May 10. Operation (ether): removal of a large piece of liver (16 *days after the first operation*). The animal is fat and all the viscera look normal.

Liver.—Microscopically there has been practically complete repair of the liver necrosis. The lobules are of normal size and general appearance. In the very center of the lobule may be seen a few round cells and a little condensation or thickening of the reticulum. A few of the liver cells in the centers of the lobule show a few fat droplets. Here and there throughout the lobules are found small foci of mononuclear cells.

May 11. Dog completely recovered.

May 22. *Chloroform* anæsthesia 2 *hours;* 0.7 *ounce* given.

May 23. *Chloroform* anæsthesia 1½ *hours;* 0.6 *ounce* given. Anæsthetic taken well and animal appears lively.

May 24. Operation (ether): abdominal incision for removal of a piece of liver. The animal bled very easily, and the hemorrhage could not be controlled. Animal died 1 hour later.

Autopsy.—Dog is very fat. The edges of the wound show a hemorrhagic œdema. The abdominal cavity contains about 300 cc. of fluid blood. There are old adhesions around the scars of former operations on the liver. Thorax, heart, and lungs are normal in gross. Microscopical sections of *heart* show a little fragmentation of the heart muscle and a very diffuse infiltration with very fine fat droplets. Thymus is normal in gross and in sections. Spleen, pancreas, stomach, and intestines are normal. *Kidneys*: the cortex is pale, and the medullary rays are conspicuous. Microscopically the straight tubules in the medullary rays contain a great deal of fat. The glomeruli, convoluted tubules, and stroma are normal.

Liver is large, pale, and fatty-looking. The cut section is quite uniform. The lobules are conspicuous, with red center and an opaque, yellow peripheral zone. The organ is quite friable. Microscopically the liver lobules show a hyaline central necrosis involving about three-fifths of each lobule. This necrosis is of the usual type. The middle zone contains a large amount of fat, and the peripheral zone of liver cells is about normal. There are a few mitoses here. A few of the lobules in their central portions show a thickened reticulum, which may contain a compact mass of mononuclear cells and a little yellow granular pigment. This is all the evidence to be found indicating the primary necrosis and repair which can be followed above in the sections. The newformed liver cells are evidently as susceptible to the chloroform as the original liver cells. The bile ducts are quite normal in all sections.

NOTE.—*This animal shows a primary central necrosis of about one-half of the liver lobule which is almost completely repaired during the following* 16 *days. A second administration of chloroform gives a similar picture. The animal appears to be slightly more susceptible. At autopsy one can find scarcely any indication of the primary chloroform necrosis, which had been produced just one month previously.*

Summary.—The process of repair in the liver lobule after an extensive chloroform necrosis may be outlined about as follows: The hyaline masses of liver cells appear quite intact and homogeneous, staining a bright pink with eosin, for 24 to 48 hours. Many wandering cells come into these areas, and the necrotic cells are rapidly dissolved and removed in great part in the next 36 to 48 hours. The mononuclear cells now predominate and may be actively phagocytic. The liver cells

show mitoses after the first 24 to 36 hours, if the animal recovers, and the mitotic figures are very numerous at the end of the second day. The columns of liver cells elongate by cell division, and fill up the empty spaces left in the reticulum by the digestion and removal of the dead liver cells. Following an extensive injury (one-half to three-fifths of each liver lobule) the repair is more than half completed in six days (Fig. 9), almost complete in eleven days (Fig. 10), and quite complete in three weeks. Such necrosis and repair does not lead to any cirrhosis.

IV. Chloroform Poisoning in Man.

This subject has been of great interest to surgeons, especially in the German hospitals, and has called out many contributions to the recent literature. The clinical picture is well known and an abstract of a typical case is given below. Comparison with the cases of chloroform poisoning in dogs shows that the processes are identical. Animals vary greatly in their susceptibility to this drug given by inhalation, and it is evident that the same rule holds for human beings. There is no known way of estimating this susceptibility in animals nor in human beings, though one can say that the amount of liver necrosis, as a rule, varies directly with the length and depth of anæsthesia and the amount of chloroform administered. Young animals are found to be more susceptible than adults. It is worthy of emphasis that the fatal case recorded below followed a minor surgical operation in which the chloroform anæsthesia lasted only 35 minutes.

Delayed Chloroform Poisoning.

D. C., female, negress, age 19 years. Surgical No. 18860.

Only a short abstract of the clinical history will be given. The patient came in because of swelling in the right axilla. Family history negative. Past history unimportant. Habits are good. The year before admission she began to have a little fever, headache, and loss of appetite. September, 1905, operation for tuberculous glands in the neck. March 5, 1906, admitted to the hospital. The lump in the right axilla has been growing slowly for the past three months. Some time ago it ruptured, and there has been a discharge for some time. There is some swelling of the right breast. Physical examination is of no particular interest and shows evidence of a tuberculous process in the right side of the neck and in the right axilla. Thorax and abdomen are quite normal. Sputum is negative for tubercle bacilli. Temperature before operation showed a daily afternoon rise to 102° or 103° F. Urine is normal.

March 10. Operation: incision and drainage of abscesses of chest wall and right axilla (Dr. Watts). *Chloroform 35 minutes.* Patient stood the operation very well and recovery from the anæsthetic was rapid. She vomited several times that night. Temperature 99.8° F.

March 11. In the morning the patient vomited dark fluid. In the afternoon when given food she immediately vomited again. The patient complained of some cramplike pains over the upper portion of the abdomen. She was quiet and rational, but did not sleep.

March 12. In the morning some muscular tremors in arms and legs were noticed. The patient is talking a good deal and is irrational at times. Vomiting continues. Vomitus is clear or slightly bile-stained fluid. Later in the day she became noisy and had to be restrained. Slight jaundice of the sclerotics noted. Urine quite normal.

March 13. The patient is irrational at times and very restless. Pulse became rather weak and respiration irregular. Jaundice is very definite in sclerotics. The patient had short convulsive attacks about 10 a. m. She became comatose as the day advanced. Respirations became more labored and rapid. Pulse became more rapid and weaker, 110 to 130 per minute. Temperature subnormal. The patient died at 6.40 p. m. *Urine* on day of death showed a trace of albumin. No sediment—a few hyaline casts. There is no acetone. Leucine and tyrosin are present in considerable amounts (Dr. Wiel).

Autopsy No. 2689. 10 a. m., March 14, Dr. Whipple.

Clinical Diagnosis.—Acute intoxication; chloroform poisoning.

Anatomical Diagnosis.—Extreme central necrosis of liver; fatty degeneration of kidneys and heart; subserous and pulmonary petechial hemorrhages; icterus; acute bronchitis; bronchopneumonia; general tuberculous lymphadenitis; tuberculous peritonitis; operation wounds.

Only that part of the autopsy protocol will be recorded which is of particular interest in relation to chloroform poisoning.

Body is that of a well-built, well-nourished colored female, 164 cm. in length. Rigor mortis is present. The sclerotics show a deep yellow jaundice tint. The pupils are equal. There are surgical incisions on the right side of the neck and in the right axilla. The peritoneal cavity is clear. The organs are normally disposed. The retroperitoneal fat is dotted over with little ecchymotic spots, some of them measuring 3 mm. in diameter. The pleural and pericardial cavities are clear.

Heart weighs 250 gm. The epicardial fat is well preserved. The chambers are dilated. The heart muscle is very pale, and has a yellowish color. All the valves are delicate, and the intima is smooth. The wall of the left ventricle averages 15 mm. in thickness. Tangential section shows a pale, uniform, yellowish brown heart muscle. There are a few minute ecchymoses below the endocardium of the left ventricle. Microscopically there is no increase in connective tissue. The muscle cells show fragmentation and fatty degeneration.

Lungs.—The pleural surfaces are smooth. The bronchi show a swollen purple mucosa. Some of the bronchial lymph glands show caseous foci. The cut section is moist, deep pink in color, mottled with irregular, purplish areas of small size not over 1 cm. in diameter. Microscopically many of the alveoli contain fresh blood and some an exudate of polymorphonuclear leucocytes and little fibrin. The blood, which is well preserved, is the striking feature of the section. *Stomach* contains a black granular material and fluid. Its mucosa is pale and smooth. *Duodenum* and *intestines* are negative, except for a few small tuberculous ulcers in the ileum. The *pancreas* is normal. Spleen, mesenteric glands, pelvic organs, brain and neck organs show nothing of importance.

Kidneys weigh 420 gm. The left kidney measures 11 x 7 x 4½ cm. The capsule comes off easily, leaving a pale, smooth surface. The cut section shows a cortex averaging 9 mm. in thickness. The striæ are quite straight. The tubular portion of the cortex is opaque and yellow. The glomeruli are visible as minute red dots. The pyramids are normal. There are a few ecchymoses in the pelvic fat. The right kidney is of similar description. Microscopically there is no nephritis. The glomeruli are normal. The convoluted tubules show a very definite fatty degeneration, and some of the epithelial cells have undergone necrosis. All of the epithelium of the convoluted tubules stains faintly. The capillaries are congested. The straight tubules show much less change.

Liver measures 25 x 17 x 8 cm. It is not enlarged. The cut section has a uniform appearance. The lobules are very conspicuous. The centers are deep red, and the margins are very

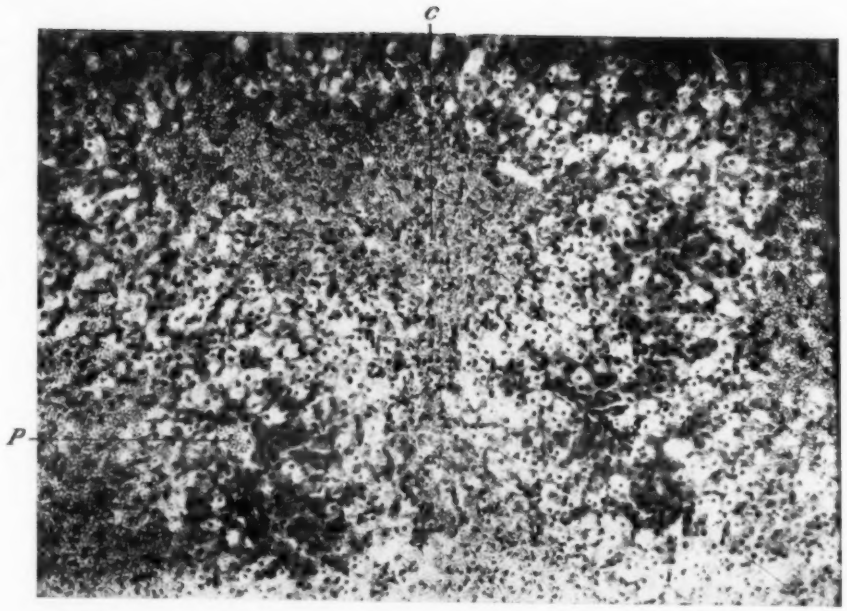


FIG. 1.—Central necrosis (chloroform) in pregnancy (dog 31). All liver cells necrotic except a row or two about the portal vein (*P*); center of lobule (*C*); a thin middle zone of fat can be seen.

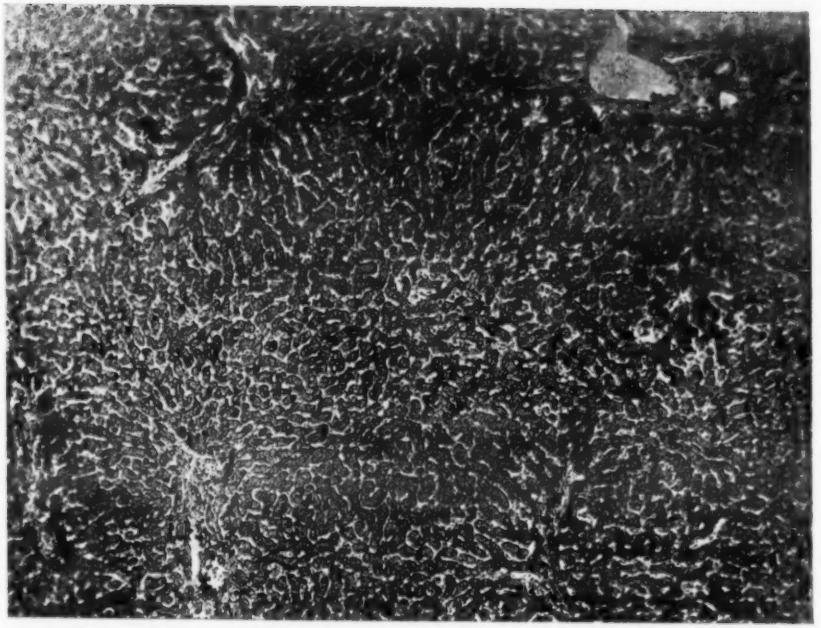


FIG. 3.—Ligation of hepatic artery (dog 38). Liver normal.

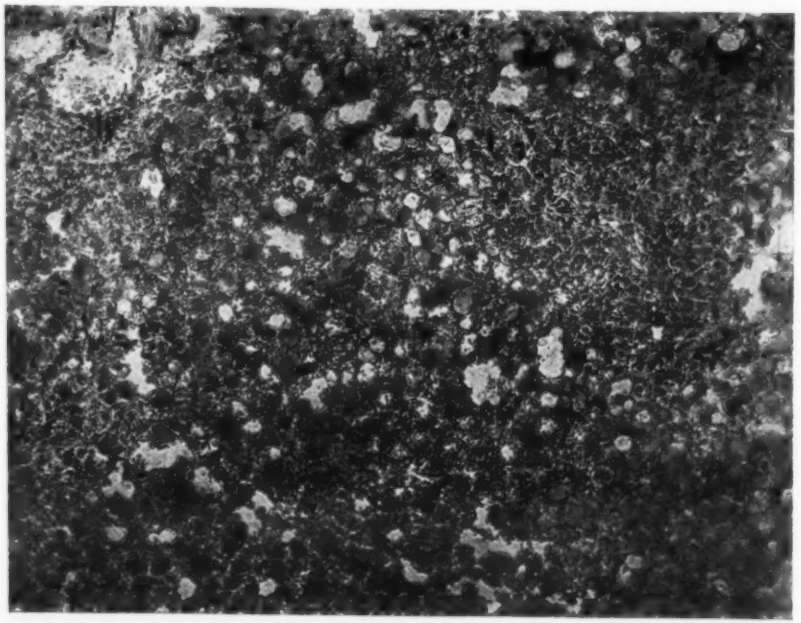


FIG. 2.—Central necrosis and extreme fatty degeneration (dog B). Chloroform anæsthesia for two hours.

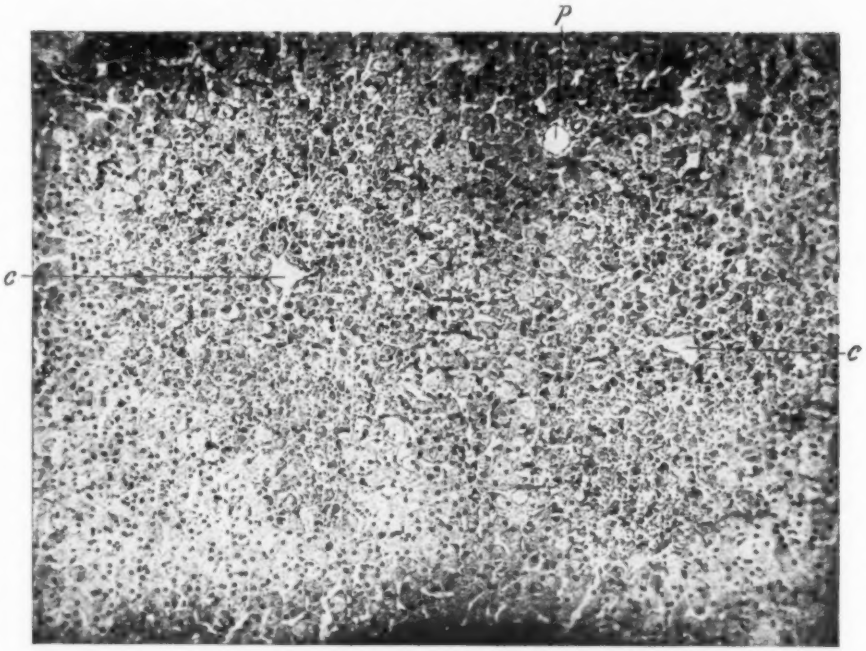


FIG. 4.—Ligation of hepatic artery (dog 37). Central necrosis (chloroform) of usual type; (*P*) portal vein; (*C*) central vein.

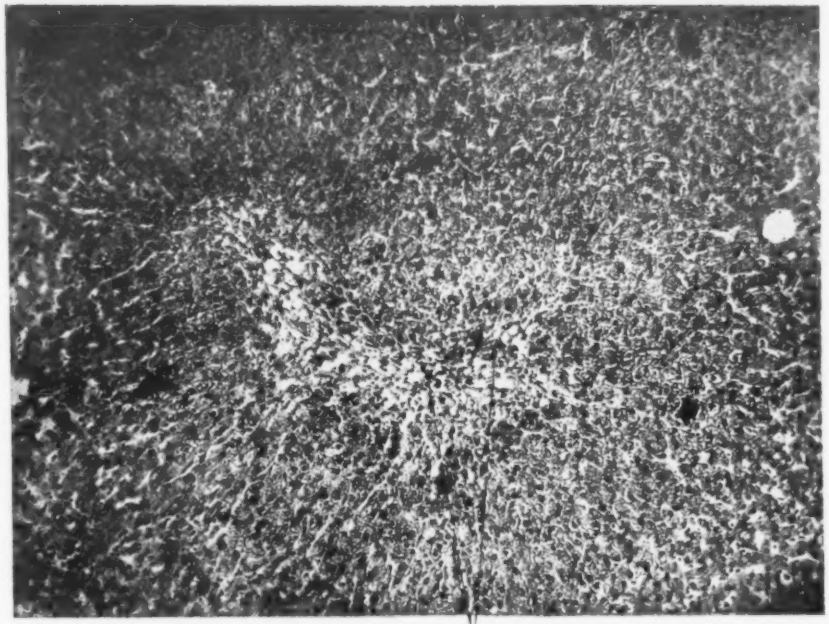


FIG. 5.—Ligation of hepatic artery (dog 37). Repair after central necrosis (eleven days); (*a*) nests of mononuclears, round, small hyaline debris.

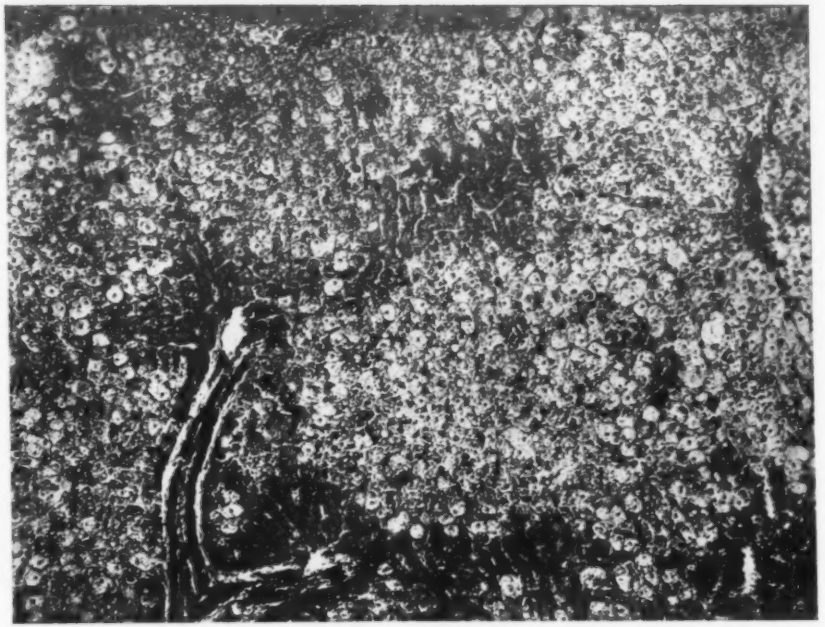


FIG. 7.—Eck fistula (dog 27). Central necrosis (chloroform) of usual type.

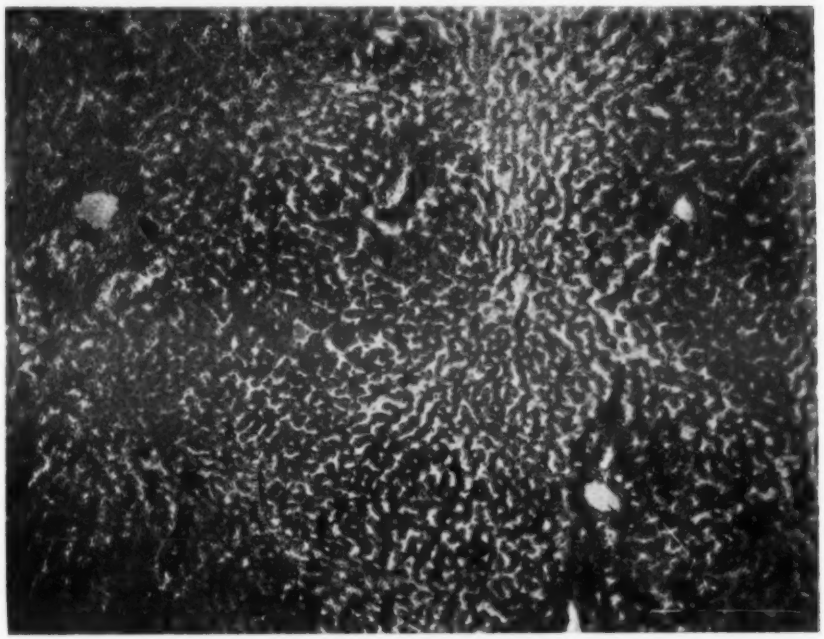


FIG. 6.—Eck fistula (dog 35). Central atrophy is evident.

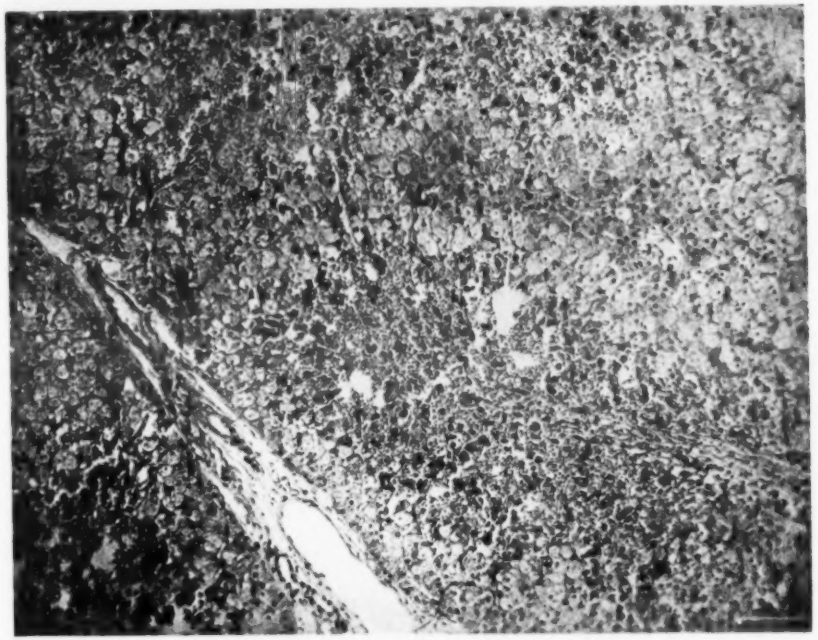


FIG. 8.—Central necrosis (dog 40). Chloroform for three hours. Fatty mid-zone is conspicuous; central three-fifths is necrotic.

Fig. 8.—Central necrosis (dog 40). Chloroform for three hours. Fatty mid-zone is conspicuous; central three-fifths is necrotic.

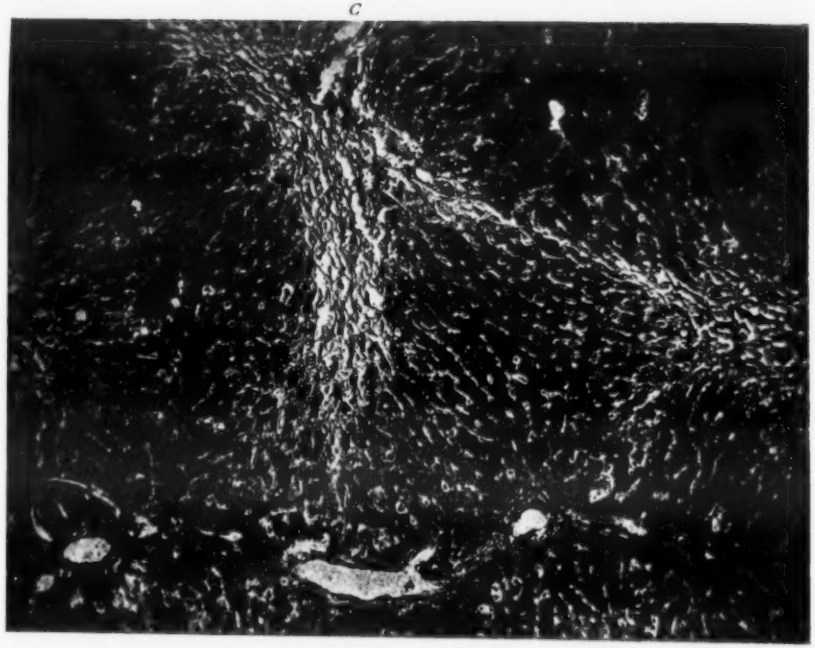


Fig. 9.—Repair at end of six days (dog 13). More than half the damage has been repaired. Empty central reticulum (*C*) left by removal of dead liver cells.

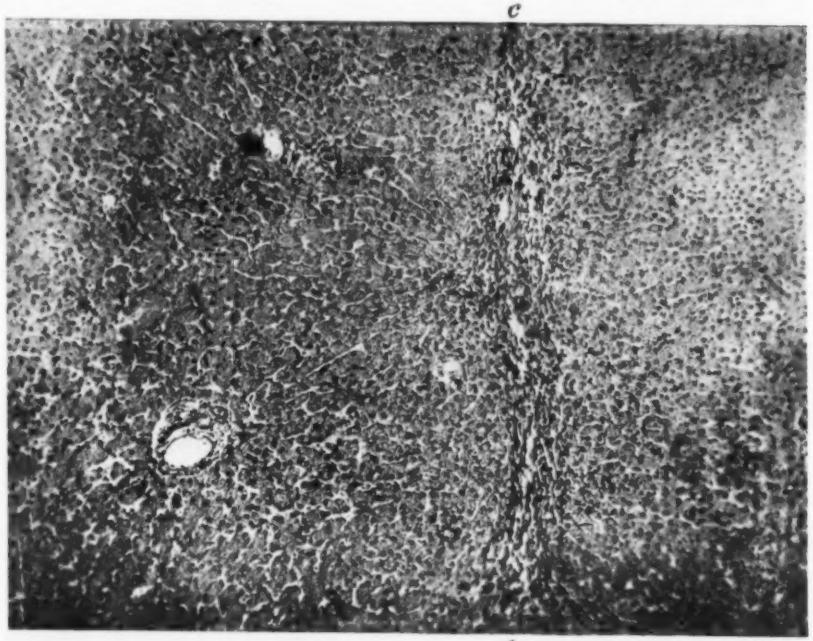


Fig. 10.—Repair at end of eleven days (dog 40). Healing of necrosis seen in Fig. 8 almost complete; many mononuclears in meshes of central reticulum (*C*).

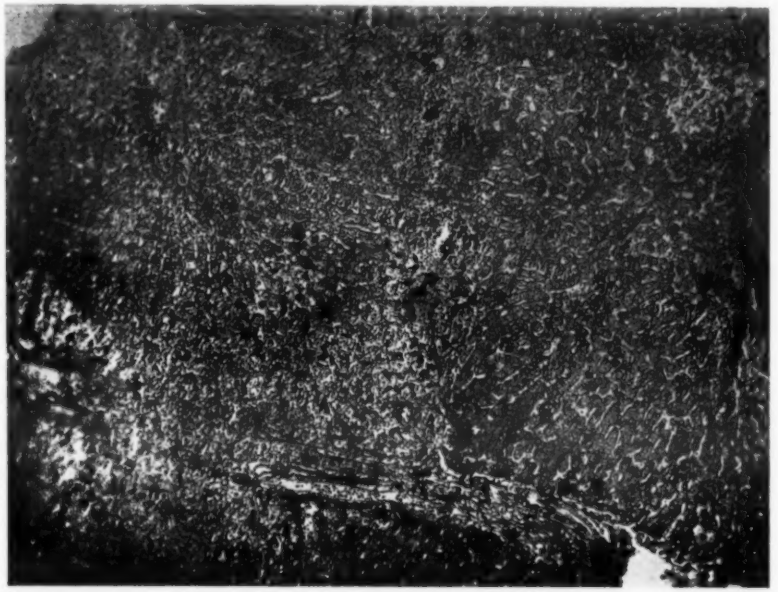


Fig. 11.—Peripheral necrosis (*P*) due to chloroform injection in portal vein (dog 23).

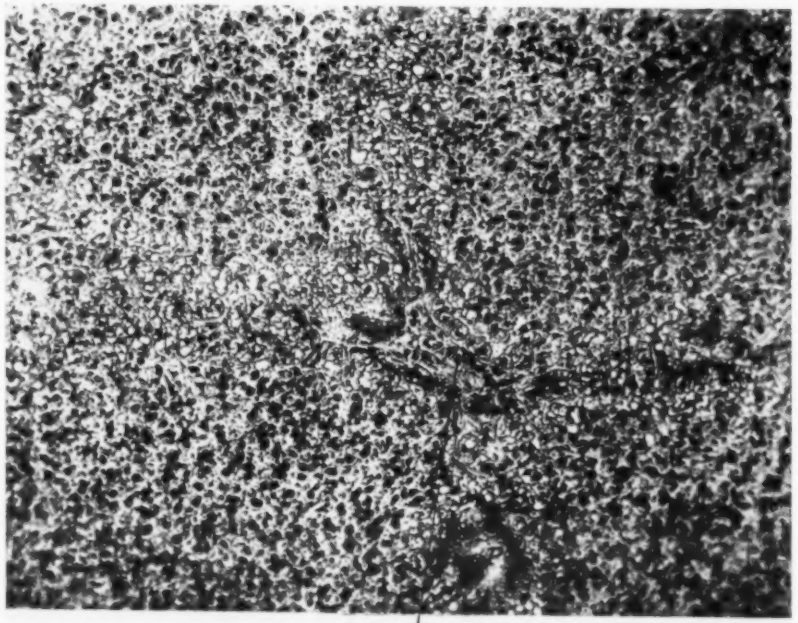


Fig. 12.—Human case (2689). Chloroform necrosis involving all but a single layer of liver cells round portal veins (*P*).

thin, sharply outlined and of a yellowish color. The consistence is rather friable. The gall bladder contains a greenish fluid bile. Its mucosa is normal. Microscopically every liver lobule shows almost complete necrosis, involving the central portions and all the liver cells except a single row about the portal spaces (Fig. 12). The remaining liver cells about the portal spaces show advanced fatty degeneration and a few mitotic figures. The areas of necrosis show complete hyaline transformation of the liver cells and invasion by the usual wandering cells (polymorphonuclear and mononuclear). There has been as yet but little solution of the hyaline material. The gall ducts are quite normal. It seems that this is a condition of acute yellow atrophy in which the etiology is clear.

General Summary.

1. Chloroform is a poison and when given to produce anæsthesia will cause more or less damage to the liver. This is true for man and animals.

2. Chloroform anæsthesia for a period of one to two hours invariably causes some central liver necrosis, and may cause a fatal result in dogs.

3. Animals vary widely in their susceptibility to this drug. Young animals as a rule are more susceptible than adults.

4. Chloroform anæsthesia for 35 minutes may cause fatal poisoning in man with almost complete liver necrosis (Fig. 12).

5. The pathology of chloroform poisoning is identical in dogs and in man.

6. The essential change is an extensive necrosis and fatty degeneration of the liver (Fig. 2). There may be numerous ecchymoses and hemorrhages into the peritoneum or upper intestinal tract. The pancreas may show many fat necroses and ecchymoses. The kidney and heart may present a moderate grade of fatty degeneration.

7. *Pregnancy* is no protection against the poisonous action of chloroform anæsthesia. Chloroform narcosis in pregnancy may cause extreme liver necrosis (Fig. 1) and placental necrosis with separation and hemorrhage. The fetuses may show no liver necrosis.

8. Central necrosis due to chloroform is uninfluenced by the blood supply of the lobule. This necrosis is the same whether the hepatic artery is ligated (Fig. 4) or the portal blood excluded by means of an Eck fistula (Fig. 7).

9. Ligation of the hepatic artery causes no change in the normal dog (Fig. 3).

10. An Eck fistula produces a diffuse atrophy and little fatty degeneration, affecting principally the centers of the liver lobules (Fig. 6).

11. Chloroform injected into the portal vein will cause scattered necroses, many of which are peripheral (Fig. 11).

12. Chloroform injected into the hepatic artery will cause necroses of the same type, both peripheral and central, the latter predominating.

13. The liver necrosis becomes visible to the microscope only after six to ten hours. The explanation for this is not clear.

14. If an animal recovers from the chloroform poisoning, the *repair* takes place rapidly and brings the liver back to normal in two to three weeks.

15. Repair is effected by solution of the necrotic liver cells and rapid multiplication of the remaining peripheral cells.

16. Repair goes on normally in a liver which is shut out from the arterial stream (Fig. 5).

17. Cirrhosis does not follow extensive central necrosis and repair (Figs. 8 and 10).

In conclusion it is our privilege to express our sincere thanks to the many men who aided us in this work: Drs. Homans and Voegtlin for the Eck fistula material, Dr. Parsons for assistance in operations, and Dr. Winternitz and Mr. Broedel for great assistance with the illustrations.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS MEDICAL SOCIETY.

April 19, 1909.

Meeting of the Johns Hopkins Hospital Medical Society, Dr. Frank R. Smith, the president, in the chair.

I. The Wassermann Reaction in the Diagnosis of Syphilis. DR. P. W. CLOUGH.

This paper will be published in the BULLETIN.

II. Diet in Typhoid Fever. DR. S. STROUSE.

Dr. Strouse drew attention to the importance of the diet in such a disease as typhoid fever, where no specific therapy exists. The feature common to all cases of typhoid fever is the fact that the course of the illness is a long drawn-out battle between the patient and the disease. It is evident that the therapeutic goal should be the strengthening of the patient to the full limit of good, without harming him. This is adopted in such diseases as tuberculosis and septicæmia. Starvation in itself is a disease with various symptoms due to disturbed metabolic processes, and if Ewing's work is correct most of the symptoms of typhoid fever are caused by somewhat similar metabolic changes.

Food at once must be considered the main weapon, and a diet should be provided with sufficient nutrition, remember-

ing the handicaps under which the patient fights. Milk, which contains all the elements of a proper food in convenient form, has long been considered the ideal diet. And yet on milk diet the loss of weight has been striking. It is estimated to amount to from 200 to 600 grams daily, made up of water, fat, and the protein of the body tissues. It is known that by artificially raising the body temperature an increase of protein metabolism occurs, but an increase in the diet will decrease protein destruction even in fever. The reason for the ordinary typhoid diet not preventing this emaciation is clear. The ordinary individual in fever expends 2800 calories per day. 1500 to 2000 cc. of milk a day supplies only 1000 to 1400 calories. The deficit in energy supplied by the food will be made up by burning the body tissues.

It is almost a traditional belief that milk and other liquids are the most easily digested and absorbed. But experiments show that absorption of the most easily digested foods including milk is 5 to 10 per cent less than in a normal individual. Further, such food as egg or meat reaches the inflamed Peyer's patches in more liquid form than milk, which enters the cardiac orifice of the stomach a liquid and leaves the pylorus a solid.

But the proof of the diet is the eating, and the actual results are the final test. The papers of Shattuck, Thayer, Litchfield, and Kinnicutt in this country call attention to these results. A comparison of 98 cases on liberal diet and 149 on liquid diet at the Johns Hopkins Hospital is in favor of the freer diet. The death rate is lower, and the incidence of hæmorrhage and perforation less. As relating to the digestibility of the respective diets, it is interesting to note that abdominal pain, nausea, vomiting, and distention are present to a less degree. The total length of the illness is shorter and the convalescence almost two days less on the average. The convalescence is less formidable; the necessary increase in diet is a far easier task; and the patient is much more comfortable. Such a liberal diet has been tested sufficiently to warrant the conclusions not only that it is not harmful, but that it offers distinct advantages over the low diet.

While details of diet cannot be prescribed by dogmatic rules, the underlying principle in feeding typhoid fever patients should be to furnish at least the same amount of food energy required by a healthy resting person.

Discussion.

Dr. W. S. Thayer.—He pointed out the difficulty in taking the other side of this question. As much nourishment should be given as the patient can take, in order to keep up the strength and prevent the loss of body weight. One cannot help feeling that the individual resistance against complications and sequellæ toward the end of an attack is much better in the well-fed, fatter, and less anemic individuals. These principles are well recognized everywhere except in the United States. The remarkable conservatism in American hospitals is strange. The reason is largely because it has been routine for so long. The general profession have accepted it without question. The country practitioner is the wiser and has the better results. He cannot feed his patients according to any rule. In some preliminary work Dr. Voegtlen showed that the loss of nitrogen to the body could be prevented absolutely by increasing the carbohydrate intake.

The reasons commonly given for not feeding are that it increases the intoxication and makes grave intestinal complications more likely. The statistics of the Russian army surgeon who fed his patients ordinary ward diet show that convalescence is shorter, the patients get up sooner, and are not so thin.

It is quite irrational to consider that there is any danger in feeding a typhoid patient. Experiment has shown there is no danger. Of course, it is unwise to overfeed any patient.

Dr. Thayer has followed Dr. Shattuck's scheme and is sure the patients do better. Body weight is saved. There is never any harm done. There is no reason for believing hæmorrhage in increased, nor does it favor perforation. The residue is not increased, and it would make no difference if it were.

Dr. Thayer said he felt very strongly upon the subject. From the standpoint of common sense it is the only course to pursue. He believes one should use common sense and not a rule. The public are frightened about feeding. But one should pay no attention to them and carry out what he thinks is best.

Dr. W. G. MacCallum.—A wave of indignation passes over me when I think of being starved and exposed to the dangers incident to starvation!

Milk becomes solid and less digestible than other foods. Everything becomes liquefied in the intestines. Cohnheim has shown that large lumps stay in the stomach until liquid, but minced meat passes through while still solid. All food must undergo the same change before reaching the ulcers. Weber has shown that the increased protein downfall in fever can be eliminated by an increased carbohydrate intake and nitrogenous equilibrium maintained. Everything points to the advantage gained by a liberal diet.

III. Exhibition of Pathological Specimens. Dr. W. G. MacCallum.

Dr. MacCallum spoke of the changes from syphilis in the trachea and bronchi. They are usually tertiary and quite serious. They develop in the mucous membrane or outside in the glands, breaking down into ulcers and loss of tissue. The destruction is more extensive than usually seen in tuberculosis. They occur in the lower trachea, near the bifurcation. Ulceration extends to the cartilages, eroding them, and is followed by scarring, distortion, and stenosis.

The rigidity of the trachea is gone and so a kinking occurs. The symptoms are those of interference with respiration.

The first specimen shown was just such a deep ulceration in the trachea with extensive granulation tissue and involvement of the glands. A syphilitic mesaortitis was associated. The woman had choked to death.

In the second specimen a syphilitic stricture was present at the bifurcation of the trachea, shutting off respiration from both lungs. A general bronchopneumonia was associated with dilatation of the bronchi. Dr. MacCallum emphasized this as one of the chief causes of bronchiectasis.

They usually result in death from prolonged attacks of dyspnœa. Operation, mercury, and the iodides give good results.

The other specimens were from three cases of occlusion of the cœliac axis with development of a collateral circulation. In the first case the superior mesenteric artery was plugged by a thrombus which developed upon a patch of arteriosclerosis. The pancreatico-duodenal and gastro-duodenal arteries were dilated, giving a good circulation. There was no sign of infarction. The second case showed the same collateral circulation by the cœliac axis. In it an embolus from the mitral valve (mitral stenosis) plugged the superior mesenteric artery.

In the third case, one of advanced arteriosclerosis, the orifice of the cœliac axis was filled with a clot in an aneurysmal sac. The cœliac axis ran alongside but was obliterated by this pressure. The collateral circulation was from the superior mesenteric artery by the pancreatico-duodenal to the branches of the cœliac axis. Again there was no sign of infarction or impaired blood supply.

May 3, 1909.

Meeting of the Johns Hopkins Hospital Medical Society, Dr. Frank R. Smith, the president, in the chair.

I. Exhibition of Surgical Cases. DR. HARVEY CUSHING.

The first case shown by Dr. Cushing was operated upon nine months ago and a tumor in the cerebellum removed satisfactorily. The patient has done well, gained 50 lbs. in weight, and is back at work. The gain in weight is probably coincident with the liberation of the secretion of the pituitary body, which the increased intracranial tension had thrown out of function. The patient walks well now. There is no headache, no choked discs, nystagmus, or ataxia. Dr. Mallory reports the tumor an encapsulated glioma, although the latter are usually looked upon as infiltrating.

The second case was operated upon 3 weeks ago. He had had a high grade of choked discs with only a little loss of vision. He is one of 4 suboccipital operations in the hospital at the present time. No growth was found but there is considerable improvement from the suboccipital decompression. He has perfect use of his neck although the cervical muscles were divided and part of the foramen magnum excised.

The third case was a carpenter, 26 years old. He complained of headaches and unsteadiness. The examination was negative. He had grown progressively worse and 8 weeks ago, in another hospital, the lateral ventricle was aspirated for a cyst. Here 3 weeks ago, the symptoms pointed to a right extracerebellar tumor. It proved to be a left intracerebellar benign cyst. The removal was successful and the patient is making a complete recovery. His vision, lost before operation, is returning.

In summary, Dr. Cushing said there were 4 such cases in the hospital now with suboccipital operations. In the other two no lesions had been found. As to statistics, of 30 known or presumed cerebellar tumor cases undergoing suboccipital exploration 3 had died. One of these died from pneumonia. There were no other complications. The tumor was found and removed in 11 cases. 3 were solid tumors, 4 cysts which were evacuated, and 4 were extracerebellar tumors. No improvement followed the removal in 2 instances. In 12 cases, no tumor was found and simple decompression was performed. In 2 of these subsequently a cyst and a solid tumor were found.

Inasmuch as these are usually regarded as most unfavorable tumors, the results are remarkably good. Dr. Cushing now considers them favorable cases.

Interesting points are:

1. The number of mistaken diagnoses. The lesion is treated often for years under the diagnosis of labyrinthine disease, gastric headaches, and hysteria.

2. The blindness. Of 11 successful extirpations, 6 were totally blind before operation.

DISCUSSION.

DR. T. B. FUTCHER.—I saw the first case in July, 1908, in consultation. He complained of nausea, vomiting, and some dizziness. There were no ocular features. He was treated for gastric disturbances without improvement. Later the failure of vision occurred and the choked discs were discovered. The importance of the cerebral origin of gastric disturbances is rightly emphasized!

II. Brain Tumors: A Preliminary Discussion with Lantern Slides. DR. CHARLES LAMBERT, New York City, N. Y.

Dr. Lambert read an elaborate paper upon the subject of brain tumors based on his study of 40 brain tumors from the New York hospitals during the last six years. His remarks were freely illustrated by lantern slides of gross and microscopical specimens.

Dr. Lambert noted that cortical tumors occurred most frequently, and tumors in the basal ganglia least so. More are in the left hemisphere than the right.

He adopted, from his analysis, a unit of growth for brain tumors consisting of a central vessel with fibroblastic arrangement about it. Then comes a neurogliar layer, and more distant the more ependymal type. The pattern is followed by the different tumors—vascular centers with fibroblastic, neurogliar, and ependymal arrangement about them. The cells orient themselves according to the nutrition with degeneration in the intermediary portion. This is the general plan of growth of the gliomata. Gliomata are essentially within the brain as compared to endotheliomata. They vary from rapid-growing embryonic tissue to mature fibroblastic type.

A series of dural tumors, endotheliomata, were shown upon the screen. Microscopically the beginnings of the tumors are seen in the endothelium lining the dura mater. The proliferation of endothelium is associated with the pursuit of vessels into the tumor. The characteristics of these tumors are the whirls or nests of proliferating cells lining the lymph and blood vessels. Pial tumors are essentially vascular, made up of vessels with thickened walls. In addition congenital cavernous angiomata were described.

Illustrations were shown of an area in the pons resembling a hæmorrhagic infarct, due to the squeezing of the pons into the foramen magnum during the sudden release of pressure by lumbar puncture. This was followed by sudden exitus.

In summary: I. Endotheliomata may be (1) dural, (2) dural and pial, mixed, (3) pial, hæmangiomata, and (4) congenital cavernous angiomata.

II. Gliomata exhibit the types of cells known as (1) ependymal, (2) neuroglial, the diffuse astrocytic cell, and (3) the marginal fibrillæ, the one or the other predominating to the submission of the rest.

Gliomata are getting back to the embryonic cell; endotheliomata are more adult.

III. Obstructions of the Inferior Vena Cava. Dr. J. Hall Pleasants.

Dr. Pleasants presented a complete analysis of the cases of obstruction to the inferior vena cava in the literature and the Johns Hopkins Hospital to date. Of 400,000 admissions to the Johns Hopkins Hospital and Dispensary there are but 16 cases recorded. 14 of these have been among the 3000 autopsies performed. Welch in 1893 reported 193 cases in the literature, and the total now is 303.

Dr. Pleasants noted that the only valve was near the heart. Slight enlargements at the renal and hepatic veins allow a division of the inferior vena cava into the lower, middle and upper thirds. The vein is more likely to be occluded by pressure as it passes behind the liver.

The occurrence is more frequent than generally supposed. As to age, a few cases are in children but the majority are after 40, in the third and fourth decades.

200 cases were due to thrombosis, and all the conditions predisposing to thrombosis are represented. Primary thrombosis is reported but the cause not determined. Thrombosis usually begins in branches and extends to the main vessel. It is commonly from the iliac veins in infectious diseases. The inferior vena cava may be the path of extension from one branch to another, as iliac to iliac. New growth was the starting-point in 21 cases, presumably by slowing the stream and increasing the chance of infection. Embolism occurred in only 2 cases.

Three cases were due to amœbic abscess of the liver, in the Hopkins series, these being the only instances found. Perforation of the inferior vena cava occurred in 2 of these.

The symptoms are often hard to differentiate from the underlying condition giving rise to the obstruction. The 2 most important are mechanical effects, namely: (1) œdema, and (2) collateral circulation.

The œdema of the feet, legs, and lower half of the body is marked. The unilateral œdema described by Schlesinger is interesting. The œdemas may be transitory. They disappear with the development of a collateral circulation. Rapid obstruction is fatal on account of the lack of collateral circulation. Dilated veins upon the legs are due to associated iliac obstruction.

The following tables show a classification of all the cases:

I. *Thrombosis*—198 cases.

A. Arising within the inferior vena cava or its branches—50 cases:

	Cases.	
1. Infectious diseases		40
Typhoid fever	15	
Scarlet fever	2	
Pneumonia	2	
Smallpox	1	
Meningitis	1	
Erysipelas	1	
Tonsillitis	1	
Cholera	1	
Tuberculosis	16	
2. Chlorosis		8
3. "Over-exertion"		2

B. Extension from localized foci of disease—108 cases:

	Cases.
1. Puerperal sepsis	36
2. Local inflammatory foci	18
3. Cirrhosis of the liver	8
4. Abscess of the liver	8
5. Trauma	17
6. New growths	21

C. Of unknown origin—40 cases:

II. *New growths from the wall of the inferior vena cava*—2 cases.

III. *Invasion of the lumen by a new growth ("new-growth thrombosis")*—46 cases:

	Cases.
1. Cancer of the kidney	13
2. Sarcoma of the kidney	6
3. Sarcoma of the "pelvis"	2
4. Cancer of the "peritoneum"	3
5. Cancer of the liver	3
6. Cancer of the parotid gland	1
7. Cancer of the testicle	5
8. Sarcoma of the testicle	2
9. Sarcoma of the vertebræ	2
10. Cancer of the uterus	1
11. Sarcoma of the ovary	1
12. Sarcoma of the "peritoneum"	1
13. New growth of undetermined origin	6

IV. *Pressure*—43 cases:

	Cases.
1. New growths	17
2. Diseases of the liver:	
Cirrhosis	3
Syphilis	7
Echinococcus cyst	6
3. Enlarged pancreas	1
4. Enlarged retroperitoneal glands	4
5. Fibrous adhesions	3
6. Aneurysms	2

V. *Kinking of the inferior vena cava*—2 cases.

VI. *Congenital*—9 cases.

VII. *Involving both the inferior and the superior vena cava*—4 cases.

The series at the Johns Hopkins Hospital includes cases of obstruction, as follows:

	Cases.
Due to embolism in typhoid fever	1
Due to thrombosis in tuberculous peritonitis	1
In puerperal sepsis	3
In amœbic abscess of the liver	3
In chronic appendicitis	1
In perirectal abscess	1
In syphilis of the liver	1
Due to congenital thrombosis(?)	1
Due to invasion by an endothelioma of the right kidney	1
By sarcoma of the lumbar vertebræ	1
By angiosarcoma of the left ovary	1
And of unknown cause	2

May 17, 1909.

Meeting of the Johns Hopkins Hospital Medical Society, Dr. Frank R. Smith, the president, in the chair.

I. Pellagra. DR. W. S. THAYER.

This paper appeared in the JOHNS HOPKINS HOSPITAL BULLETIN, July, 1909.

II. Etiology of Movable Kidney. DR. F. WEBB GRIFFITH.

This paper will be published in the BULLETIN.

III. Treatment with Tuberculin in the Dispensary. DR. LOUIS HAMMAN.

This paper appeared in the JOHNS HOPKINS HOSPITAL BULLETIN, August, 1909.

IV. Subcutaneous Purgatives—A Clinical Study on Phenoltetrachlorphthalein. DR. L. G. ROWNTREE. (From the Pharmacological Laboratory and the Medical Clinic of the Johns Hopkins University.)

The need of a subcutaneous purgative is pointed out. An ideal subcutaneous purgative must possess the following properties: It must act on the intestinal tract and on the intestinal tract only without any untoward effect on any other organ or system, must act with certainty, must be readily soluble (preferably in water) in order that the amount of fluid to be injected may be small, and it must be non-irritant locally. As a rule, it should produce its effect within a short time, although in some conditions an action delayed in onset but prolonged in character is to be preferred.

The literature dealing with the question of subcutaneous purgatives is reviewed. The different substances heretofore utilized for this purpose are contrasted with the ideal purgative described above, and their value in this field is discussed.

It is shown that although intestinal peristalsis is undoubtedly increased by some, at least, of the salines, yet the increase in activity is not sufficiently marked to result in purgation unless toxic or lethal doses are injected. The salines, therefore, are of no practical importance to medicine as subcutaneous purgatives.

Its toxicity and the wide-spread nature of its activity preclude the general adoption of barium chloride in this field.

The vegetable purgatives, such as aloes, colocynth, cathartinic acid, oleum ricini, and oleum tiglii, although possessing the power of inducing purgation, are debarred from this field on account of the marked irritation they produce at the point of injection.

Among alkaloids, apocodeine hydrochlorate in doses of .02 gm. to .05 gm. is a serviceable hypodermic purgative in many instances, but is unsatisfactory inasmuch as it is uncertain and involves systems and organs other than the alimentary and is somewhat too irritant locally.

Eserine undoubtedly has its place in practical therapeutics in warding off intestinal paresis following abdominal operations, in expelling gas from a distended intestine and in overcoming intestinal atony following parturition, but it is an exceedingly powerful alkaloid and must be used judiciously. It can never come into general use as a subcutaneous purgative.

More information must be furnished as to the mode of preparation and as to the chemical properties of podophthalyl before it can be further investigated. No clinical reports have as yet been published.

Phenoltetrachlorphthalein is next considered and the method of making its oil preparation described. A brief outline of the manner of its absorption and excretion and its mode of action is given.

A table is presented showing the results obtained by its subcutaneous administration in 0.2- and 0.3-gm. doses (10 and 15 cc. of the oil preparation) to five patients in the obstetrical ward. These results, though not entirely satisfactory, indicate that this drug possesses decided laxative value and that its laxative action is of a prolonged character.

Another table is presented showing its effect when 0.4 gm. (20 cc. of the oil preparation) is given hypodermically to patients suffering from chronic constipation. Ten out of twenty-five patients after receiving one injection of this oil preparation together with instructions as to diet, hygiene, and habit have had no return of constipation, although at least two months and in some instances as many as six months have elapsed since its administration.

The draw-backs in the way of the general adoption of phenoltetrachlorphthalein as a subcutaneous purgative are:

1. The insolubility of this drug in water.

2. The slight degree of its solubility in oil, necessitating a large volume for injection.

3. The long time that elapses before the onset of purgation (18 to 24 hours).

4. The mild character of its action, which is laxative rather than purgative.

Its redeeming features:

1. The prolonged nature of its action.

2. The absence of crampy pain and colic throughout the period of its action.

3. Its non-irritant effect locally.

4. The constancy, at least in the cases so far studied, with which it has produced its result.

5. The non-toxicity of the drug.

Phenoltetrachlorphthalein is efficient, non-toxic and non-

irritant when administered as a subcutaneous purgative, but its insolubility in water and its low solubility in oil stand in the way of its wide application, as such, in practical therapeutics, but do not detract from its efficiency when a subcutaneous purgative is indicated. It may prove of value:

1. In coma.
2. In marked gastrointestinal irritability when nothing can be given by mouth.
3. Among the insane, who often refuse to swallow medicine and who fight against enemata.
4. In chronic constipation, together with hygienic, dietetic and psychical treatment.

It is worthy of a trial in the field of abdominal surgery, where its introduction beneath the skin can be accomplished during the anæsthesia without any pain whatever and where its mild, prolonged, laxative effect, continuing for from four to six days, may possibly entirely dispense with the necessity of administering any purgative by mouth during the first week subsequent to the operation.

THE LÆNNEC.

March 22, 1908.

Meeting of the Lænnec Society for the Study of Tuberculosis, Dr. H. B. Jacobs, the president, in the chair.

I. Tuberculosis of the Liver. Dr. W. S. Thayer.

This patient, a colored woman, aged 49, was operated upon for a tubo-ovarian abscess in 1892. Last fall she was admitted with fever and tenderness in the right upper abdomen. There was an indefinite resistance in the liver region at first and gradually it became palpable. The irregularly remittent fever and absence of leucocytosis suggested tuberculosis, and, with the suggestion of adherent intestines, a diagnosis of tuberculous peritonitis was made.

She had just recently returned with diarrhœa, fever, sweats, and a rapid loss of strength. Both apices and different parts of the lungs were involved. The liver was large, firm, and smooth. Last night she died, and the autopsy to-day showed fresh pulmonary tuberculosis. There was a marked caries of the sixth dorsal spine. The tuberculous peritonitis was adhesive, walling off cavities containing chyliform fluid (the third such case this year). The liver shows a most interesting picture. Through the surface white nodules are visible, and on section the tissue is studded with white, raised areas—a translucent ring around a caseous center. It is a nodular tuberculosis of the liver.

The case is striking, first, on account of the rarity of so extensively caseating a tuberculosis of the liver in a woman of 49, and second, because the prominent symptom clinically was the enlarged liver.

Discussion.

Dr. W. H. Welch.—It would be interesting to get out the type of tubercle bacillus. It may be bovine, but the chances are against it. Weigert, years ago, pointed out this peculiar cirrhosis of the liver in the presence of tubercles with more or less ascites. They are on the order of solitary tubercles, only more numerous. It is difficult to localize the primary focus in this case.

Dr. M. C. Winternitz.—There were numerous desquamated epithelial cells in the fluid, but no tubercle bacilli.

II. A Study of Recent Educational Leaflets. Dr. Chas. J. Hatfield, Philadelphia.

The speaker summed up the qualities of a desirable leaflet for lay perusal bearing upon pulmonary tuberculosis. He pointed out the hopefulness of popular education as a means of prevention of the disease. Exhibitions with demonstrations of the cause, prevention, and means of treatment of tuberculosis were first instituted at the Johns Hopkins Hospital. And it is encouraging that the people are anxious to be taught what can be done in prophylaxis. The enormous attendance at exhibitions in New York and Philadelphia recently are evidence of this.

To be useful a leaflet must be comprehensive. It must outline the predisposing causes. It must emphasize alcohol as the agent of lowered resistance in the chronic habitual drinker. The exciting cause, a short description of the bacillus, the methods of infection as inhalation of dust, food, drink, break in the skin, must all be included. The early symptoms should be made plain, and stress must be laid upon all the essentials of cure. The value of fresh air and the lack of danger in the night air and draughts; the value of foods, with a list of cheap nutritious foods; rest, the avoidance of overwork or fatigue—these are all important.

No consumptive was ever harmed by two much rest; many are by over exercise. The layman should be warned against the quack who traffics in human lives.

But the most important part of such a leaflet is that dealing with prevention:

1. The care of the sputum.
2. The care of the house.
3. The care of the patient's body.
4. The care of intermediate objects.

It is important to state that the careful patient is not a danger to those about him. Co-operation with the State laws should be emphasized. Finally there should be added a list of dispensaries, sanatoria, with the hours for treatment.

So much for the ideal educational leaflet!

Discussion.

Dr. H. B. Jacobs.—I want to emphasize the value of such papers to students. They are not to be heard elsewhere. These are things which it is important to have come within the knowledge of students.

III. Marmorek's Serum in the Treatment of Pulmonary Tuberculosis. Dr. Wolman.

See Article No. 3 in the Johns Hopkins Hospital Bulletin, August, 1909.

Discussion.

Dr. C. V. Pirquet.—In Vienna we obtained the same results as most clinics, and found no effect, good or bad, with this serum. The theory is a good one, but it does not work. This is not a problem which will be solved by finding a serum at all. Grüner injected a combination of tuberculin and

Marmorek's serum subcutaneously. It had no more effect than so much water. The fact that rectal injection is possible shows the serum has no effect. If antidiphtheric serum is given per os or rectum, no antitoxin is absorbed.

DR. W. H. WELCH.—Prof. A. E. Wright holds that an accidental amount of tuberculin is the only value in Marmorek's serum. McClintock has pointed out that digestion can be inhibited with sodium bicarbonate and opium so that absorption of antitoxin can occur.

IV. The Employment of Arrested Tuberculous Cases. DR. FORSTER.

See Article No. 4 in the JOHNS HOPKINS HOSPITAL BULLETIN, August, 1909.

DISCUSSION.

DR. HATFIELD.—It is important that the colony should be self-supporting, if possible. The large proportion of patients are able to stand work. At White Haven the work is graduated—one hour at first, increasing one half hour every week. As the work was increased, it was found the strength had, up to six hours a day. But all the heavier work must be done by healthy individuals.

The Phipps Institute, at Philadelphia, employs the arrested cases as nurses for advanced cases. Twenty-two such individuals have been graduated from a two-year course and are now occupying profitable positions nursing tuberculous cases.

DR. HUNNER.—Do you encounter any prejudice in disposing of the fruits of the colony?

DR. FORSTER, in reply: The surplus products are sold in wholesale markets in the mornings without question. A higher price is obtained because of the care in selection and packing. They are also sold in the town of Towson without question. At Eudowood graduated patients are also employed as trained nurses with success.

The announcement of the Lænnec Prize was then made. (See the JOHNS HOPKINS HOSPITAL BULLETIN, May, 1909.)

The election of officers for the ensuing year resulted in the re-election of Dr. Henry Barton Jacobs as president, and Dr. Louis Hamman as secretary.

BOOKS RECEIVED.

Experimental Pharmacology. A Laboratory Guide for the Study of the Physiological Action of Drugs. By Charles Wilson Greene, Ph. D. Third edition, revised. With 37 new illustrations. 1909. 8vo. 76 pages. P. Blakiston's Son & Co., Philadelphia.

Hydrotherapy. A Brief Summary of the Practical Value of Water in Disease. By William H. Dieffenbach, M. D. 1909. 8vo. 267 pages. Rebman Company, New York.

City of New York. Department of Public Charities. City Hospital, Blackwell's Island. Medical and Surgical Report. Number 1, 1909. 4to. 237 pages. Martin B. Brown Company, New York.

Legal Medicine and Toxicology. By R. L. Emerson, A. B., M. D. (Harvard). 1909. 8vo. 593 pages. D. Appleton & Company, New York and London.

Studies of Criminal Responsibility and Limited Responsibility. By Charles Follen Folsom, A. M., M. D. 1909. 8vo. 153 pages. Privately printed.

The Principles and Practice of Medicine. By William Osler, M. D. Seventh edition, thoroughly revised. 1909. 8vo. 1143 pages. D. Appleton & Company, New York and London.

Modern Medicine. Its Theory and Practice. In original Contributions by American and Foreign Authors. Edited by William Osler, M. D. Assisted by Thomas McCrae, M. D. Volume VI. Diseases of the Urinary System—Diseases of the Ductless Glands—Diseases of Obscure Causation—Diseases of the Muscles—Vasomotor and Trophic Disorders—Life Insurance. Illustrated. 1909. 8vo. 799 pages. Lea & Febiger, Philadelphia and New York.

Archives of Neurology and Psychiatry. From the Pathological Laboratory of the London County Asylums, Claybury, Essex. Edited by Frederick Walker Mott, M. D., F. R. S., F. R. C. P. Vol. IV. 1909. 8vo. 330 pages. P. S. King & Son, Westminster.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by W. T. Longcope, M. D. Nineteenth series. Volume II. 1909. 8vo. 301 pages. J. B. Lippincott Company, Philadelphia and London.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D.; assisted by H. R. M. Landis, M. D. Volume II. June, 1909. 8vo. 317 pages. Lea & Febiger, Philadelphia and New York.

A Text-book of the Diseases of the Ear. By Professor Dr. Adam Politzer. Translated at the personal request of the author and edited by Milton J. Ballin, Ph. B., M. D., and Clarence L. Heller, M. D. Fifth edition, revised and enlarged. With 337 original illustrations. 1909. 8vo. 892 pages. Lea & Febiger, Philadelphia and New York.

L'Hypophyse et la Médication Hypophysaire. (Étude Expérimentale et Clinique.) Par M. le Docteur Arthur Delille. 1909. 4to. 336 pages. G. Steinheil, Paris.

Children in Health and Disease. A Study of Child-Life. By David Forsyth, M. D., D. Sc. With frontispiece. 1909. 8vo. 362 pages. P. Blakiston's Son & Co., Philadelphia.

A Manual of Operative Surgery. By Sir Frederick Treves, Bart. G. C. V. O., C. B., LL. B., F. R. C. S., and Jonathan Hutchinson, F. R. C. S. Third edition, with new colored plates and many new illustrations in the text. Volume I. 1909. 8vo. 775 pages. Lea & Febiger, Philadelphia and New York.

Saint Thomas's Hospital Reports. Edited by Dr. H. G. Turney and Mr. W. H. Battle. New series. Volume XXXVI. 1907. 8vo. 390 pages. 1909. J. & A. Churchill, London.

Tuberculosis. A Preventable and Curable Disease. Modern Methods for the Solution of the Tuberculosis Problem. By S. Adolphus Knopf, M. D. 1909. 12mo. 394 pages. Moffat, Yard & Company, New York.

Myomata of the Uterus. By Howard A. Kelly and Thomas S. Cullen. Illustrated by August Horn and Hermann Becker. 1909. 4to. 723 pages. W. B. Saunders Company, Philadelphia and London.

Dietetics for Nurses. By Julius Friedenwald, M. D., and John Ruhräh, M. D. Second edition, revised and enlarged. 1909. 12mo. 395 pages. W. B. Saunders Company, Philadelphia and London.

Oxford Medical Publications. Publishers: Henry Frowde, London; Hodder & Stoughton, London. The following 8 volumes:

Studies on Immunity. By Robert Muir, M. A., M. D., in collaboration with Carl H. Browning, M. D., Alexander R. Ferguson, M. D., and William B. M. Martin, M. B., Ch. B. 1909. 8vo. 216 pages.

Common Disorders and Diseases of Childhood. By George Frederic Still, M. A., M. D. (Cantab.), F. R. C. P. (Lond.). 1909. 8vo. 731 pages.

Medical Inspection of Schools. By A. H. Hogarth, M. B., B. Ch., Oxon., D. P. H. 1909. 12mo. 360 pages.

Graphic Methods in Heart Disease. By John Hay, M. D., M. R. C. P. With an introduction by James Mackenzie, M. D., M. R. C. P. 1909. 12mo. 184 pages.

Inborn Errors of Metabolism. The Croonian Lectures delivered before the Royal College of Physicians of London, in June, 1908. By Archibald E. Garrod, D. M., M. A. Oxon. 1909. 12mo. 168 pages.

Suture of Arteries. An Experimental Research. By E. Archibald Smith, M. B., Ch. B. Victoria University, F. R. C. S., England. 1909. 8vo. 70 pages.

The Blood in Health and Disease. By R. J. M. Buchanan, M. D., F. R. C. P. 1909. 8vo. 318 pages.

Aseptic Surgery. By Charles Barrett Lockwood, F. R. C. S. Third edition. 1909. 12mo. 275 pages.

Bulletin of Iowa Institutions. (Under the Board of Control.) Published quarterly. Volume X. 1908. 8vo. 344 pages. Des Moines, Iowa.

Treatment of the Diseases of Children. By Charles Gilmore Kerley. Second edition, revised. 1909. 8vo. 629 pages. W. B. Saunders Company, Philadelphia and London.

Nothnagel's Practice. Diseases of the Intestines and Peritoneum. By Prof. Dr. Hermann Nothnagel. Edited, with additions, by H. D. Rolleston, M. A., M. D., F. R. C. P. Second edition, thoroughly revised. Authorized translation from the German, under the editorial supervision of Alfred Stengel, M. D. 1907. 8vo. 1059 pages. W. B. Saunders Company, Philadelphia and London.

Pye's Surgical Handicraft. A Manual of Surgical Manipulations, Minor Surgery and Other Matters Connected with the Work of House Surgeons and Surgical Dressers. Fifth edition, revised and largely rewritten by W. H. Clayton-Greene, B. A., M. B., B. C. (Cantab.), F. R. C. S. (Eng.). With 343 illustrations and plates newly drawn for this edition. 1909. 8vo. 592 pages. John Wright & Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent & Co., Ltd., London.

Mental Medicine. Some Practical Suggestions from a Spiritual Standpoint. Five Conferences with Students at the Johns Hopkins Medical School. By Oliver Huckel, S. T. D. With an Introduction by Lewellys F. Barker, M. D. 1909. 12mo. 214 pages. Thomas Y. Crowell & Company, New York.

The Ophthalmic Year Book. Volume VI. Containing a Digest of the Literature of Ophthalmology with Index of Publications for the Year 1908. By Edward Jackson, A. M., M. D., George E. de Schweinitz, A. M., M. D., Theodore B. Schneideman, A. M., M. D. Illustrated. 1909. 8vo. 415 pages. The Herrick Book and Stationery Company, Denver, Colo.

Principles of Pharmacy. By Henry V. Arny, Ph. G., Ph. D. With 246 original illustrations. 1909. 8vo. 1175 pages. W. B. Saunders Company, Philadelphia and London.

Bier's Hyperemic Treatment. In Surgery, Medicine and the Specialties. A Manual of its Practical Application. By Willy Meyer, M. D., and Prof. Dr. Victor Schmieden. Second revised edition, enlarged. Illustrated. 1909. 8vo. 280 pages. W. B. Saunders Company, Philadelphia and London.

Arthritis Deformans: Comprising Rheumatoid Arthritis, Osteo-Arthritis and Spondylitis Deformans. By R. Llewellyn Jones, M. B., Lond. With thirty-eight full page plates. 1909. 8vo. 365 pages. John Wright & Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent & Co., Ltd., London.

Surgical Diagnosis. By Alexander Bryan Johnson, Ph. B., M. D. Volume I. With one colored plate and two hundred and fifty-seven illustrations in text. 810 pages. Volume II. With three colored plates and two hundred and fifty-three illustrations in text. 777 pages. 8vo. 1909. D. Appleton & Company.

Atlas of the External Diseases of the Eye. Including a Brief Treatise on the Pathology and Treatment. By Prof. Dr. O. Haab. Authorized translation from the German. Third edition, revised. Edited by G. E. de Schweinitz, A. M., M. D. With 101 colored lithographic illustrations on 46 plates. 1909. 12mo. 244 pages. W. B. Saunders Company, Philadelphia and London.

NOTES ON NEW BOOKS.

International Clinics. Vol. I. 19th Series. (*Philadelphia and London: J. B. Lippincott Company, 1909.*)

There are a number of exceptionally interesting papers in this volume; one by Howard, of Montreal, who has collected all the cases of Mikulicz's disease, and carefully studied and analyzed them, and given the first satisfactory description of this disease in its relation to allied conditions; others by Duval and Vinard on "Sporotrichosis," by F. A. Richardson on "Excision of the Hip-joint in Arthritis Deformans," and MacCallum on "Absorption from the Peritoneal Cavity." The volume, in addition to its usual sections on Treatment, Medicine, Surgery, etc., with its contributions by European as well as American practitioners, has three chapters on the "Progress of Medicine during 1908." "Treatment" is handled by Stevens, "Medicine" by Edsall and "Surgery" by Bloodgood. The first volume of the new series makes an excellent beginning.

Studies in Puncture Fluids. A Contribution to Clinical Pathology. By O. C. Gruner, M. B., London, Clinical Pathologist at the General Infirmary, Leeds. 289 pages. (*Philadelphia: P. Blakiston's Son & Co., 1908.*)

It is partly on account of the author's investigations, but mainly because of the excellent collection of data from the literature on "puncture fluids," that the present volume will prove serviceable. The fluids have been studied very fully, as the following headings from the sections of the work will indicate: (1) The Chemical Examination of Puncture Fluids; (2) The Physico-Chemical Examination of Puncture Fluids; (3) The Characters Possessed by Various Puncture Fluids; (4) The Differential Diagnosis of Exudates from Transudates; (5) Cytodiagnosis. The final section details analyses of various pleural and peritoneal fluids. As a work of reference, the present volume should prove of great value in the more exact examination of exudates and transudates.

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